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A COMPARISON OF GASTRIC EMPTYING AND SECRETION OF ACID AND PEPSIN FOLLOWING HIGHLY SELECTIVE AND SELECTIVE VAGOTOMIES IN DOGS

by

© MARSHALL CHARLES HUNTING

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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OF MASTER OF SCIENCE

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled A COMPARISON OF GASTRIC EMPTYING AND SECRETION OF ACID AND PEPSIN FOLLOWING HIGHLY SELECTIVE AND SELECTIVE VAGOTOMIES IN DOGS submitted by MARSHALL CHARLES HUNTING in partial fulfilment of the requirements for the degree of MASTER OF SCIENCE in EXPERIMENTAL SURGERY.

DEDICATION

To Floss, who supervised the first knot I ever tied;
To Mom, whose strength saw me here;
To Andrea, whose promises have all come true, and
To Jamey, our hope for tomorrow.

The search for truth is in one way hard
and in another easy,
For it is evident that no one can master
it fully, nor miss it wholly,
But each adds a little to our knowledge
of nature,
And from all the facts assembled, there
arises a certain grandeur.

- Aristotle

ABSTRACT

The "ideal" operation for the surgical treatment of peptic ulcer would reduce acid secretion and maintain normal emptying and yet be free of the sequelae of dumping, diarrhea and ulcer recurrence. The search still continues for such a procedure.

Both selective and, more recently, highly selective vagotomy have been suggested as alternatives to truncal vagotomy. Selective vagotomy involves denervation of the stomach only and, unlike truncal vagotomy, preserves the vagal parasympathetic innervation to the remainder of the gastrointestinal tract. Highly selective vagotomy differs only in that the innervation to the gastric antrum (via the nerves of Latarjet) is also preserved and only the acid-secreting, parietal cell mass area of the stomach is denervated.

Using a rather unique "whole stomach" preparation in conscious dogs, this project was designed to determine the effects of selective and highly selective vagotomies on the gastric emptying of liquids and secretion of acid and pepsin. All the highly selective vagotomies were accomplished with a "no-touch" technique to ensure the function of the nerves of Latarjet to the antrum.

Although effective in preserving normal gastric emptying, highly selective vagotomy was ineffective in reducing pentagastrin stimulated acid and pepsin secretion. By contrast, selective vagotomy caused a decrease in basal and maximal acid secretion and pepsin secretion. It did, however, cause slower gastric emptying which was

overcompensated for by the addition of pyloroplasty.

A likely explanation is that the careful surgical technique prevented neuopraxial injury to the nerves of Latarjet during highly selective vagotomy, thereby ensuring the results recorded were due in fact to highly selective vagotomy and not to an inadvertent selective vagotomy.

The results suggest that the nerves of Latarjet are of prime importance in the regulation of both emptying and secretion and lend an air of mystery to the exact function of the nerve supply to the parietal cell mass.

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It seems more and more that medical research is taking the "team approach". Though never organized as such, I wish to thank the members of my "team", without whom this work could never have been accomplished:

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CHAPTER I

INTRODUCTION

A. The Problem

It is estimated that five to ten percent of the adult population of North America will suffer the symptoms of peptic ulcer at some period during their lifetime! Ultimately a certain proportion of these patients will require surgical treatment either for failure of conservative therapy or for the complications of their disease.

B. The Aims of the Solution

The "ideal" operation for the treatment of peptic ulcer, particularly duodenal ulcer, must meet several criteria:

(1) It must effectively reduce both the basal and the stimulated secretion of hydrochloric acid by the stomach - permanently. It is widely believed that such a reduction of acid output will ultimately allow the ulcer to heal;

(2) It must conserve the maximum amount of otherwise healthy uninvolved tissue according to the basic surgical concepts of Halstead;

(3) The tissue preserved must function as physiologically normal as possible after operation in order to prevent sequelae due to the operation *per se;*

(4) It must be relatively simple to perform in a uniform

manner from patient-to-patient, and;

(5) It must have a low morbidity and mortality rate.

The search for such a "Utopian" procedure has occupied the minds of gastric surgeons and researchers for over a hundred years and still continues in earnest today.

C. The History and Results of Potential "Solutions"

1. History

a. The Early Attempts

Prior to the turn of the last century, the operative treatment of peptic ulcer was almost entirely resectional. Many immutable contributions were made to gastric surgery during this era, particularly by Professor Theodor Billroth and his students. Although these techniques were practiced as late as the 1940's, the results were dissatisfying because of high rates of morbidity and mortality. They are mentioned briefly only for completeness and will not be discussed further.

b. The History of Vagotomy and Drainage

It was Sir Benjamin Brodie in 1814 who first noted a profound gastric secretory response following vagal nerve stimulation. This was subsequently confirmed by Claude Bernard (1858) who also observed a depression of gastric secretion after division of the vagus nerves in the laboratory animal. Bernard's observations were also confirmed by other physiologists, notably by Pavlov (1910).

One of the earliest descriptions of transabdominal vagotomy

is attributed to Exner and Schwartzmann (1914). The indications for these early procedures were usually functional gastrointestinal disease or tabetic crises and they were crude indeed, often incomplete, seldom uniform and by-and-large performed without cognizance of the actual physiologic effects to be expected. It is interesting, however, that even at this early stage, the atonic effects of vagotomy were recorded and successive authors reported complementary drainage procedures (Latarjet, 1922 - pylorectomy; Schiassi, 1925 - gastroenterostomy; Winkelstein and Berg, 1938 - partial resection).

This early work went unheeded until 1943 when Dragstedt and Owens reintroduced the concept of total vagal denervation of the stomach and its beneficial effect on healing of duodenal ulcers. Thereafter vagotomy became, and has remained, an essential part of the surgical treatment of acid-peptic disease.

In the 1940's and early 1950's however, it was generally felt that truncal vagotomy alone was unsatisfactory because of severe gastric stasis resulting from the loss of coordinated motor function of the antrum and pyloric sphincter spasm. As well, the rate of recurrent ulceration, particularly gastric, was high. The addition of some type of procedure to drain the denervated stomach was obviously necessary and led to such combinations as vagotomy and gastroenterostomy (Dragstedt, 1947); vagotomy and pyloroplasty (Weinberg, 1956); vagotomy, segmental resection and pylorotomy (Wangansteen, 1959); and the "combined physiological operation" of vagotomy, antrectomy and gastroduodenostomy (Harkins, 1960).

The addition of these drainage procedures, while solving

problems on the one hand, served also to create whole new classes of complications on the other. The "Dumping Syndrome" was generally ascribed to rapid passage of carbohydrate-rich fluid into the upper small bowel because of the loss or destruction of the pylorus. Post-gastrectomy weight loss, loss of the reservoir function of the stomach, and vitamin B_{12} deficiency anemia are now well recognized. Moreover, any drainage procedure increases the incidence of morbidity and mortality due to the inherent possibility of suture-line leakage or breakdown. Even an apparently simple procedure like pyloroplasty carries an increased risk to the patient if mechanical problems such as ulceration on the anterior wall, duodenal cap scarring, or difficulty in mobilizing the duodenum are encountered by the surgeon.

As experience with total truncal vagotomy increased, complications other than gastric inertia were recognized. Post-vagotomy diarrhea was ascribed to denervation of the small intestine concomitant with gastric denervation but this opinion was far from universal. Considerable disagreement raged even to its exact incidence with some reports (Harkins *et al*, 1963) quoting a frequency of nearly 70% of all patients undergoing the truncal operation. Post-vagotomy atrophy of the mucosa of the stomach and small intestine was also soon recognized. The latter was often given in account as the cause of the sprue-like syndrome which followed truncal vagotomy.

Post-truncal vagotomy biliary stasis has also been reported (Johnson and Boyden, 1952) and Reynolds, in a personal communication to Dr. C. Griffith, 1961 (quoted by Harkins and Nyhus, 1962) noted a "definite increased incidence of gall stones after vagotomy" in a

careful review and long-term followup of post-vagotomy patients. Obviously, the ideal operation had not yet been found.

In 1948, Franksson of Sweden, and Jackson of the United States, independently evaluated the operation of selective vagotomy. This operation was designed to denervate only the stomach and to preserve vagal supply to the remainder of the upper and middle parts of the gut. No drainage procedure was used initially in these series and the results were consequently disappointing when gastric inertia occurred postoperatively. Franksson soon abandoned the procedure in favor of subtotal resection.

Interest in selective vagotomy was revived in North America by Dr. C.A. Griffith of Seattle who has reported exhaustive trials, both experimental and clinical, based on a thorough understanding of the surgical anatomy of the intra-abdominal vagus (see Chapter II).

The rationale behind the introduction of selective vagotomy was carried a step farther when, in 1957, Griffith and Harkins introduced the operation of "partial gastric vagotomy". This procedure known alternatively by a host of synonyms [highly selective vagotomy, parietal cell (mass) vagotomy, proximal gastric vagotomy, acid-fundic vagotomy, etc.], involves sectioning of only those vagal fibers that pass directly to the parietal cell, acid-secreting part of the stomach, and preserves intact not only the hepatic and celiac divisions of the vagal trunks (apropos selective vagotomy) but also the vagal innervation to the antrum (the anterior and posterior nerves of Latarjet). It was hoped that preservation of the nerve supply to the antrum would maintain the coordinated muscular activity necessary for normal

emptying and so prevent the morbidity associated with mandatory complementary drainage procedure.

"On the drawing board", highly selective vagotomy approached the "ideal". Anatomically and physiologically it made sense because only that part of the stomach responsible for acid secretion was denervated - that part responsible for normal emptying was left undisturbed. Moreover, no tissue (other than nerves) was resected and if the theory was correct, postoperative acid secretion should have been reduced and emptying should have been preserved.

2. Results

a. Selective Vagotomy

Following its reintroduction in 1957, this operation underwent extensive clinical trials by many authors. According to Griffith, the main advantage of selective vagotomy over truncal vagotomy is the degree of "completeness" of vagal denervation achieved (Griffith, 1967). This premise was borne out by a number of reports which compared the results of postoperative insulin tests in controlled series of selective versus truncal vagotomy. Kraft *et al* (1962) reported a 5% incidence of positive (both early and late) insulin tests after selective vagotomy compared with twice that incidence (10%) for truncal vagotomy. A similar trend (lower incidence of positives after selective than after truncal) was reported by the authors of two exhaustive, randomized and prospective comparative studies of the two operations (Sawyers *et al*, 1967; Kennedy and Connell, 1969).

A study similar in design was reported by Mason *et al* (1968) in which a higher incidence of positive insulin tests followed selective

vagotomy, thereby casting some doubt on Griffith's contentions. An interesting point was raised therein by the authors and warrants some comment here. Initially, this particular trial was randomized but the protocol was soon abandoned in the light of a very high early incidence of incomplete results (positive insulin tests), almost 38%. It was felt that the surgeons involved in the study needed more technical experience with the selective operation which they then proceeded to obtain. Thereafter, in the latter part of the study the incidence of positive post-selective insulin tests dropped to 18.2%, causing the authors to suggest that surgical experience is important in achieving completeness of vagotomy with the selective technique.

Although there appeared to be general accord with Griffith's views concerning "completeness", there were reports of fairly high rates of positive insulin results after selective vagotomy, varying from 23 to 41% (Sawyers *et al*, 1967; Mason *et al*, 1968; Kallehauge and Amdrup, 1969; Dignan, 1970; Kronborg *et al*, 1970; Coupland and Cumberland, 1971). These results must be viewed in the light of considerable non-uniformity between series in terms of surgical experience (as above) and indications for surgery, the type of drainage employed, the technique and criteria of interpretation of the insulin tests, length of followup, etc.

A second advantage of selective vagotomy over truncal vagotomy soon came to light - the incidence of post-vagotomy diarrhea appeared lower. This was naturally ascribed to preservation of small intestinal innervation via the celiac branch and was a common feature of any

report of comparative trials (Kraft *et al*, 1962, 1967; Smith and Farris, 1963; Harkins *et al*, 1963; Sawyers *et al*, 1967; Scheinin and Inberg, 1967; Dignan, 1970; Inberg, 1970; Kronborg *et al*, 1970).

Selective vagotomy appeared to be as effective as truncal vagotomy in reducing basal and maximal acid outputs in the few trials where acid studies were undertaken. Kraft *et al* (1962) demonstrated a reduction in 12-hour overnight acid secretions from 43 mEq/12 hours to 4 mEq following truncal vagotomy and from 56 mEq/12 hours to 5 mEq following selective vagotomy. Sawyers *et al* (1968) employed the same test and reported that 80% of their truncal vagotomy patients were anacid postoperatively compared with 84% of their selectively denervated patients. Using the augmented histamine test, four groups of investigators (Mason *et al*, 1968; Kallehauge and Amdrup, 1969; Dignan, 1970; Kronborg *et al*, 1970) reported nearly identical results - both truncal and selective vagotomy reduced postoperative maximal acid outputs to histamine to about 60% of its preoperative value, and there was no significant difference between the two procedures in this regard.

A consideration for the future of this operation is an observation of a potential advantage that grew out of experimental examination. Shiina and Griffiths (1969) in evaluating selective vagotomy without drainage in dogs with Heidenhain pouches, noted a slight increase in pouch secretion postoperatively. This increase was doubled when the same animals underwent truncal vagotomy, even though the (subjective) degree of gastric retention was the same. These results were subsequently confirmed in another series in which the dogs had previously undergone pyloroplasty (Everett and Griffith,

1970). These results confirmed earlier observations by Landor (1964) and similar observations by Stening and Grossman (1970). Griffith postulated that preservation of the hepatic and celiac vagi somehow had an inhibitory effect (intestinal, humoral?) on gastric secretion, which was lost by total vagal division (Griffith, 1969). This concept has yet to be substantiated, but if true, would certainly add to the advantages of selective over truncal vagotomy.

There are several disadvantages to the selective operation. Postoperative gastric inertia has already been mentioned, and most authors have combined the operation with their "favorite" drainage procedure.

The most disturbing problem after selective vagotomy is a high incidence of the dumping syndrome. Reports of its frequency range from 19 to 39% compared with 8 to 29% for truncal vagotomy in the same series (Harkins *et al*, 1963; Smith and Farris, 1963; Kraft *et al*, 1967; Sawyers *et al*, 1967; Kronborg *et al*, 1970). Whether this complication can be ascribed to the vagotomy or to the drainage procedure employed is conjectural, and no satisfactory explanation for its occurrence has been advanced. Burge *et al* (1969) have undertaken a trial of bilateral selective vagotomy without drainage in patients with minimal or no duodenal narrowing in an attempt to reduce the incidence of the dumping syndrome. They report encouraging early results and state that "the degree of retention after operation is no greater in those patients with selective vagotomy without drainage and without organic stenosis than in those with selective vagotomy and pyloroplasty". Results of long-

term followup studies in these patients have not yet been reported and are awaited with anticipation.

b. Highly Selective Vagotomy

".... highly selective vagotomy without drainage is the first operation in the history of gastric surgery to leave the patient quite free from the sequelae we all know so well".

- H. Burge, 1972.

Of all the operations devised to date for the surgical treatment of peptic ulcer, highly selective vagotomy most closely approaches the "ideal". It appears to be as effective as truncal or selective vagotomy in reducing postoperative acid secretion. Average basal acid output is reduced by a range of 40 to 97.3% in different series and reports of pentagastrin-stimulated maximal acid output quote a decrease ranging from 51 to 72% (Amdrup and Jensen, 1970; Johnston and Wilkinson, 1970; Wilkinson *et al*, 1972; Imperati *et al*, 1972; Kragelund *et al*, 1972a&b; Johnston *et al*, 1973a). Similar results are reported for histamine-stimulated postoperative secretion (Bombeck *et al*, 1970; Miller *et al*, 1971; Hedenstedt *et al*, 1972). Johnston of Leeds, England, and Amdrup of Copenhagen, Denmark, have recently published a report (Johnston *et al*, 1973a) in which 63 patients were studied more than one year after highly selective vagotomy. Basal acid output was reduced by 80% from preoperative levels and maximal pentagastrin-stimulated output by 55% in these patients. During the first postoperative year, these values tended to fluctuate but those last reported were considered permanent.

In the only study reported of postoperative pepsin secretion, Johnston and Wilkinson (1970) reported a 51% decrease in patients tested three months after surgery.

In their original experimental introduction of the procedure, Griffith and Harkins (1957) reported that "in no instance was gastric stasis as marked following partial gastric vagotomy as it was following total vagotomy". Subsequently, several groups, using a variety of techniques (mostly radiological), have reported no change in postoperative motility or emptying (Amdrup and Griffith, 1969; Interone *et al*, 1971; Kragelund *et al*, 1972). Others reported a slight increase in the rate of gastric emptying (Clarke and Williams, 1971; Kelly and Kennedy, 1971; Hedenstedt *et al*, 1972) while Imperati *et al* (1972) report that 8% of their patients had minimally delayed postoperative emptying.

Is highly selective vagotomy effective in completely denervating the parietal cell mass? If the early results of the insulin test are used as a criterion, then the answer is yes. Postoperative insulin tests judged by various criteria were negative in 65 to 100% of patients in different series (Amdrup and Jensen, 1970; Johnston and Wilkinson, 1970; Amdrup and Kragelund, 1971; Wilkinson *et al*, 1971; Johnston *et al*, 1972; Wastell *et al*, 1972; Johnston *et al*, 1973), thereby indicating a high rate of "completeness".

As suggested by Burge, the operation appears to be remarkably free of postoperative sequelae. Humphrey *et al* (1972) evaluated patients from the Leeds group in a study of the incidence of dumping and diarrhea after highly selective vagotomy and compared the rates to other patients (non-randomized, retrospective) who had undergone

truncal or selective vagotomy. Subjectively, they found that only 6% of patients complained of symptoms suggestive of the dumping syndrome one year after highly selective vagotomy without drainage compared to 20% after truncal vagotomy with pyloroplasty and 34% after selective vagotomy, also with pyloroplasty. Fifteen "representative" patients from each group were then fed a meal of hypertonic glucose following which 47% of patients with highly selective vagotomy had symptoms compared with 73% and 80% for truncal and selective vagotomy respectively.

In a study of the frequency of diarrhea in the same groups of patients, Humphrey *et al* (1971) reported spontaneous symptoms in 2% of patients after highly selective 20% after truncal and 18% after selective vagotomy. The incidence of "urgent" diarrhea following the oral hypertonic glucose meal was 13%, 66% and 60% respectively. Hedenstedt *et al* (1972) reported "no troublesome diarrhea or dumping", and Amdrup and Jensen (1970) reported no diarrhea after operation in their first 22 patients.

The operative mortality rate of the procedure is low. Holle (1969), in a report of 171 cases followed for more than seven years, quotes an over-all mortality rate of 1.75%. If only elective cases were considered, the mortality rate dropped to zero. Moreover, his recurrence rate was a mere 0.5%.

Interone *et al* (1971) demonstrated that dogs that had undergone highly selective vagotomy required four times as long to develop gastroduodenal ulceration in response to daily injections of histamine in beeswax as did normal animals, or animals that had undergone selective vagotomy or antral denervation alone.

These results so far presented form convincing evidence for the validity of highly selective vagotomy in peptic ulcer therapy. However, there are drawbacks which have prevented its universal acceptance. Many surgeons argue that the procedure is tedious and time-consuming. There is, in addition, an on-going debate about the necessity for routine complementary drainage. Experimentally, some authors (Griffith and Harkins, 1957; Amdrup and Griffith, 1969; Kelly and Kennedy, 1971; Interone *et al*, 1971) feel such drainage is not mandatory, whereas others (Klempa *et al*, 1971) feel that motility is impaired enough to warrant such a procedure.

Clinically, the same controversy exists. Several groups (Johnston and Wilkinson, 1969; Amdrup and Jensen, 1970; Clarke and Williams, 1971; Burge, 1972) do not routinely employ drainage while others (Bombeck *et al*, 1970; Wastell *et al*, 1972; Holle, 1969; Miller *et al*, 1971) argue in favor of such a procedure.

Highly selective vagotomy appears to reduce the neural component of gastric secretion, but not the hormonal. Amdrup and Griffith (1969) reported a 47% increase in Heidenhain pouch secretion after postoperative insulin stimulation, a response which was abolished in a subsequent series of antrectomized dogs. They ascribed this to increased levels of circulating gastrin as a result of a decreased antral inhibition of gastrin release by acid. This assumption was recently proved correct by Jaffe *et al* (1972) who demonstrated a two-fold increase in circulating gastrin in patients in a basal state following highly selective vagotomy. The significance of this elevated hormone level remains to be determined.

By far the most perplexing observation following highly selective vagotomy is the high rate of reversion of once-negative early post-operative insulin tests to positive in patients tested 3 to 12 months or more after their surgery. Amdrup and Kragelund (1971), reporting on 110 patients of which 97% were originally negative, found a reversion-to-positive rate of 57% (including both early and late positive responses) in only 55 of those same patients retested a year later. Hedenstedt *et al* (1972) reported a 45% increase at one year, and Johnston *et al* (1973b) have recently reported a 51% rate. All these authors are quick to point out that although the test is positive, the rates of acid secretion remain low. For instance, Johnston's group notes that the insulin-positive patients secreted 3.9 mEq/hour of acid on the average under insulin stimulation a year after surgery compared with 33 mEq/hour preoperatively. This high reversion rate has been generally ascribed to vagal reinnervation of the parietal cell mass but direct anatomical evidence for this assumption has not yet been published.

D. The Objectives of the Project

With all this background knowledge just presented in mind, this project was undertaken to attempt to answer the following questions:

(1) Does highly selective vagotomy effectively reduce both basal and maximal acid secretion and pepsin secretion from the stomach?

(2) What are the changes, if any, in gastric emptying following highly selective vagotomy - is emptying in fact maintained so near-normal that the routine exclusion of a complementary drainage

procedure is justified?

(3) Is highly selective vagotomy effective in completely denervating the entire parietal cell mass?

(4) What are the changes invoked in emptying and secretion by selective vagotomy with or without pyloroplasty, and

(5) Would the changes observed after conversion of a highly selective vagotomy to a selective vagotomy allow some insight into the physiological function of the nerve supply to the antrum?

CHAPTER II

THE ANATOMY OF THE VAGUS NERVES

Performance of selective or highly selective vagotomy depends on a knowledge of the anatomy of the distribution of the tenth cranial nerve(s) to the abdominal viscera. To the anatomical purist this is a complex subject and in this discussion, the finer points concerning the variabilities of structures and relations will be sacrificed for a simpler understanding of the more constant aspects.

The abdominal vagal trunks (in the dog) are composed of about 35,000 fibers in total, 90% of which are afferent (sensory) and only 10% are efferent (motor). Approximately 65% of all the fibers which pass through the esophageal diaphragmatic hiatus are destined for the stomach (unpublished data, quoted by Harkins *et al*, 1963) (Fig. 1). The remainder of the fibers are distributed by the hepatic (10%) and the celiac (25%) divisions (see below) to most of the remainder of the gastrointestinal tract.

Below the pulmonary hilae, the right and left vagus nerves divide and reunite to form the peri-esophageal vagal plexus. Usually just above the diaphragm, two or more large nerve trunks emerge from this plexus to pass through the esophageal hiatus into the abdomen. The "right" vagal trunk (right and left are used hereafter to refer to anatomical position, not origin since either trunk is known to be composed of fibers from both the right and left tenth cranial nerves) usually lies posterior to the esophagus in the hiatus and the left

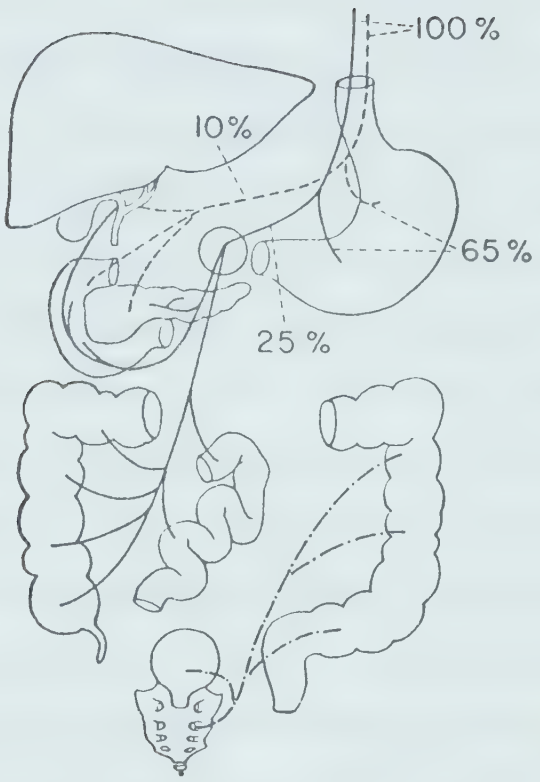

Figure 1 The differential distribution of vagal fibers to the abdominal viscera.

(Harkins *et al*, 1963)

trunk anterior, a position which is somewhat variable.

1. The Anterior Vagus

At the level of the esophageal hiatus, the left or anterior vagal trunk gives off the hepatic division (one or more branches) which passes to the right and courses anterior to the caudate lobe of the liver high in the lesser omentum to the porta hepatis (Fig. 2). At this level, a small twig or twigs descend(s) to innervate the pyloric region - the pyloric branch. Mitchell (1941) claims these pyloric branches are invariably supplied by the anterior vagal trunk only as the terminal gastric branches of the posterior system fail to reach the pylorus.

After giving origin to the hepatic division, the anterior trunk continues as the anterior nerve of Latarjet and passes inferiorly, closely applied to the lesser curve of the stomach, past the incisura angularis to end by division into terminal branches in the antrum. To the left of the nerve of Latarjet, most frequently arising from it but occassionally arising directly from the anterior vagal trunk, pass the gastric branches (4 to 10 in all) to the parietal cell mass of the stomach. These branches may run in association with terminal branches of the left gastric vessels or lie independently on the surface of the stomach before penetrating the gastric musculature at about the junction of the medial 1/3 and lateral 2/3 of the stomach.

2. The Posterior Vagus

The posterior vagal trunk is notoriously variable in its position within the esophageal hiatus (Harkins *et al*, 1963) but at the level of the left gastric artery on the posterior surface of the

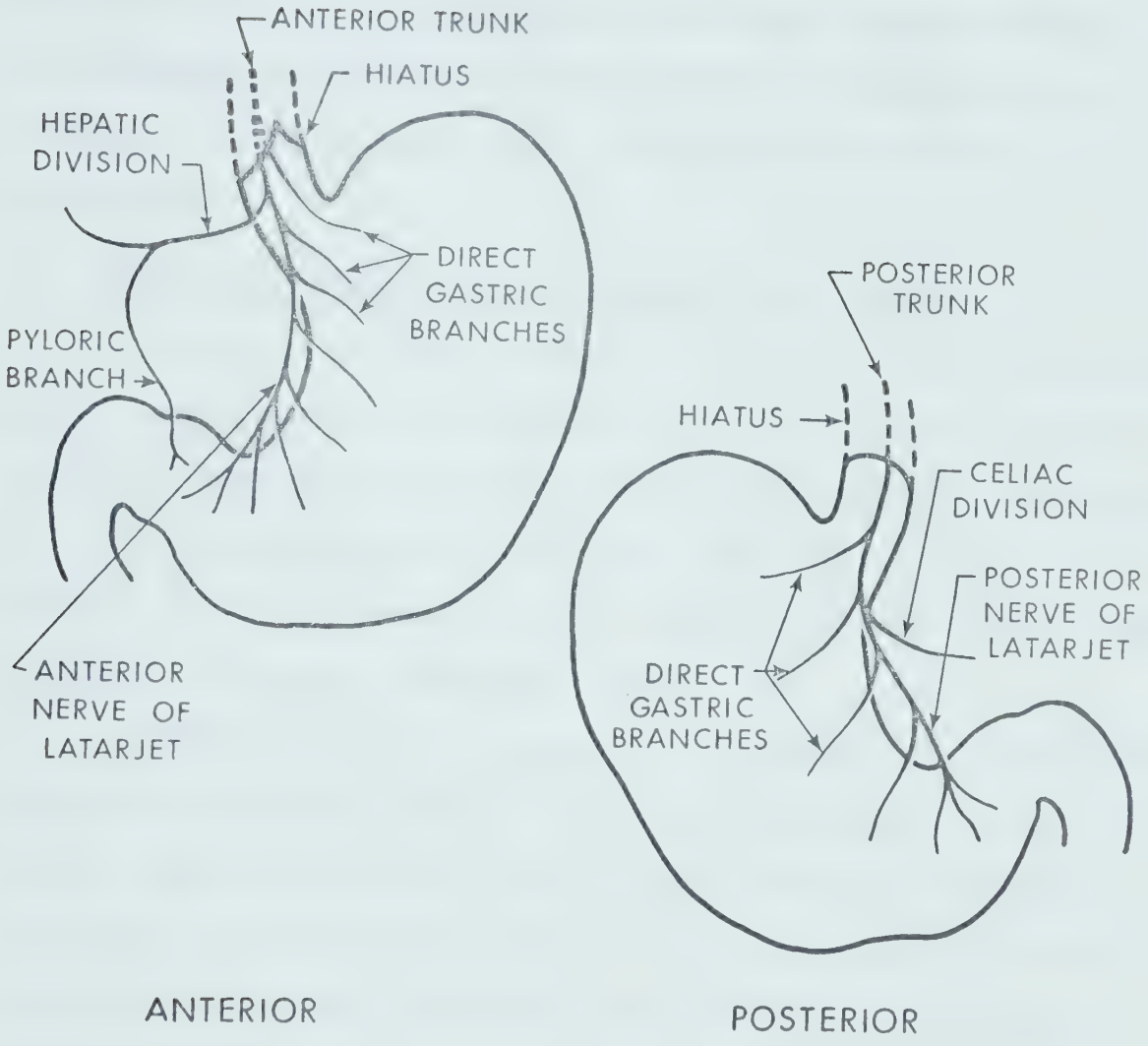

Figure 2 The distribution of the vagus to the stomach

stomach its position is constant. It is here that the large celiac division begins and descends posteriorly in association with the left gastric artery to the celiac plexus from whence it is distributed to the remainder of the embryological foregut and the entire midgut. The remainder of the posterior trunk comprises the posterior nerve of Latarjet which is distributed in a like manner to its anterior counterpart.

3. Physiological Distribution of the Vagus in the Abdomen

Stavney *et al* (1963) undertook a study of the vagal distribution of the gastrointestinal tract by measuring mechanically the changes in motility invoked by electrical stimulation of various vagal components.

Simultaneous stimulation of both vagal trunks increased motility all the way down to the right ascending colon, including stomach, duodenum, gallbladder, jejunum and ileum.

Following selective vagotomy (gastric branches cut, hepatic and celiac branches intact), only the response in the stomach was lost. On another preparation, if only the gastric branches were stimulated (no distinction was made between gastric branches *per se* and the nerves of Latarjet to the antrum) the response was localized to the stomach and proximal duodenum.

Stimulation of the hepatic branch produced increased motor activity of the gallbladder and proximal duodenum (presumably via the pyloric branch) only. Celiac division stimulation invoked changes in the proximal and distal duodenum, the entire small bowel and the ascending colon. In addition, marked changes were seen in the gall-bladder, a result the authors ascribed to artifactual duodenal

contraction. This finding could probably better be explained by Mitchell's (1941) demonstration that some fibers of the hepatic division may be contributed by the posterior system.

McCrea (1924-25) and Mitchell (1941) both demonstrated after dissection of several species that the anatomic distribution of the vagus in the dog and man is similar, so one is apparently justified in drawing conclusions based on studies in either species.

CHAPTER III

METHODS AND MATERIALS

A. The Model

The dog has traditionally served as the model for investigation of gastrointestinal secretion. Of more importance in its choice for this project was the demonstration of McCrea (1924-25) and later by Mitchell (1941) that the anatomic distribution of the vagal system in the abdomen of the dog was analogous to the human.

Ten healthy adult mongrel dogs (eight female, two male; average weight 24.9 kg) were used throughout the entire project. They were housed in the Health Sciences Vivarium at the University of Alberta and were allowed outside in specifically designed runs for daily exercise. Each was fed a standard diet of one can of Dr. Ballard's Champion commercial dog meat per day. Water was given *ad libitum*. In addition, they received supplemental salt and occasional supplemental vitamins *per os*.

B. Protocol

This project was executed in five stages (Fig. 3):

1. Stage I - Control

All ten animals underwent a left lateral cervical esophagostomy. Following recovery, control measurements of gastric emptying and basal and stimulated secretion were performed. As well, a "control" insulin

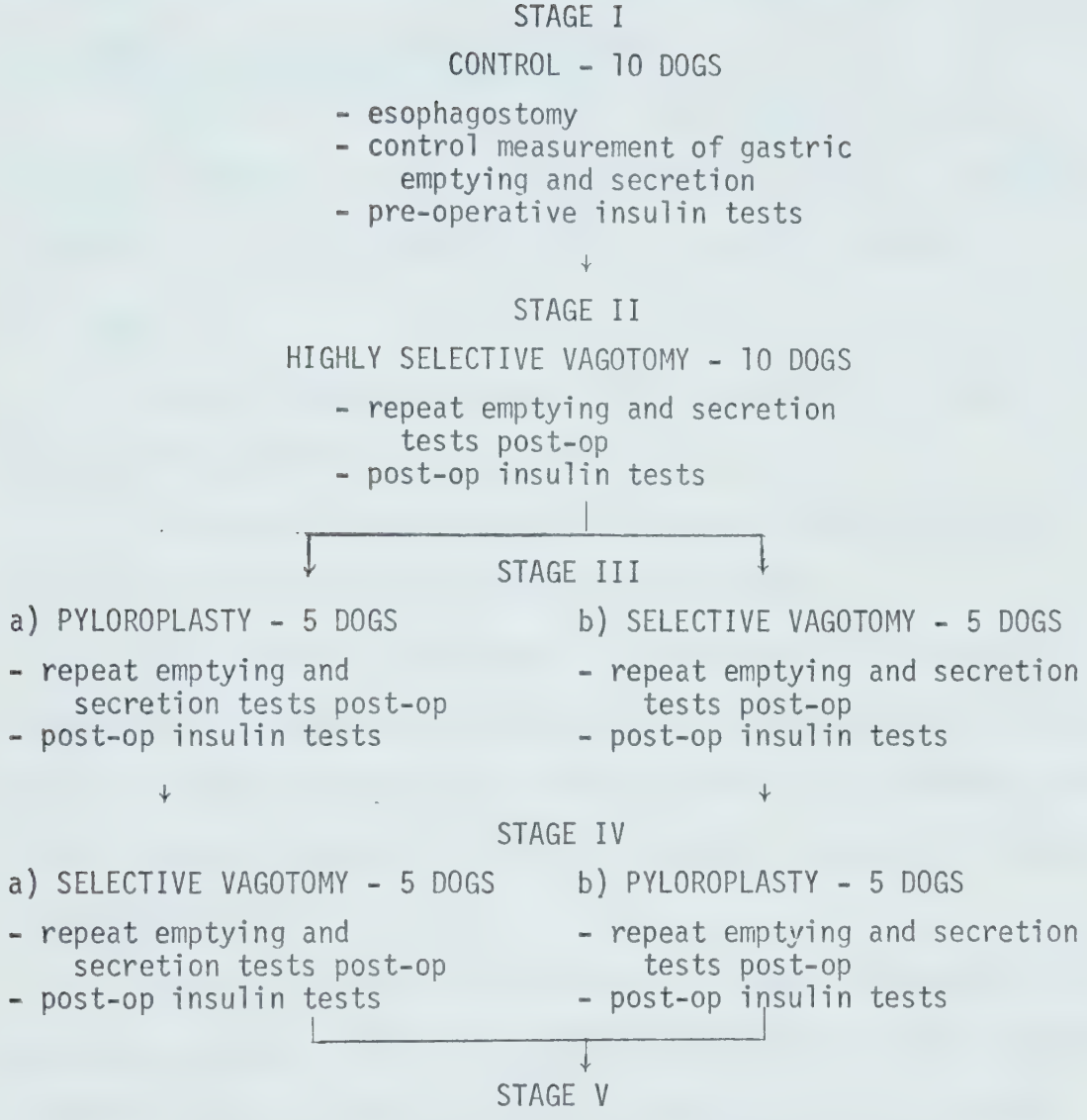

Figure 3 Outline of Protocol

test was done on each animal prior to Stage II surgery.

2. Stage II - Highly Selective Vagotomy

The same ten dogs from Stage I were subjected to highly selective vagotomy using the technique described below. Following recovery, the tests of emptying and secretion were repeated.

3. Stage III

Prior to Stage III surgery, the ten animals from Stage II were randomly divided into two groups.

The choice of operation for each group (either selective vagotomy or pyloroplasty) was also made at random.

The five animals in Stage IIIa underwent a pyloroplasty in an attempt to provide evidence to resolve the dispute as to whether or not a routine complementary drainage procedure was necessary after highly selective vagotomy. Following recovery, the tests of emptying and secretion were repeated.

The other five animals, assigned to Stage IIIb underwent a selective vagotomy. This stage allowed comparison of highly selective vagotomy without drainage to selective vagotomy without drainage. In addition, it allowed insight into the physiological function of the nerves of Latarjet to the antrum by studying emptying and secretion before and after these nerves were sectioned.

4. Stage IV

Stage IV was also divided into two parts - a and b, and represented a direct continuation of Stages III - a and b, respectively.

The rationale for Stage IV was similar to Stage IIIb in that

it provided evidence in regard to the function of antral innervation. It also created another category of operation for comparison, that of selective vagotomy with drainage.

Stage IVb was designed to test whether or not complementary drainage was necessary with selective vagotomy and to provide additional data on the operation of selective vagotomy with drainage.

It was during Stage IV that a deviation from the protocol was necessary. Testing following Stage IIIb indicated that in three of the five dogs, denervation of the antrum was probably incomplete. After discussion it was felt it would be wiser to alter the protocol to ensure completion of Stage IIIb rather than to proceed to Stage IVb in these particular animals. Consequently, those three "incompletely denervated" animals underwent laparotomy in Stage IVb to determine whether residual innervation to the antrum had been left at Stage III surgery. In one dog, both anterior and posterior nerves of Latarjet were found intact. In the other two, only one nerve in each dog was intact, both anterior. The remaining two animals in Stage IVb underwent pyloroplasty according to the original protocol. All five animals in Stage IVa were selectively vagotomized.

By the end of Stage IV, there existed four combinations of denervation with/without drainage operations:

1) highly selective vagotomy without drainage - 10 dogs
2) highly selective vagotomy with pyloroplasty - 5 dogs
3) selective vagotomy without drainage - 5 dogs
4) selective vagotomy with pyloroplasty - 7 dogs

5. Stage V - Pre-terminal Studies of Completeness of Vagotomy

The final stage consisted of a simple test (see below) to determine whether or not any residual innervation remained to the parietal cells of the stomach. Following completion of this stage, all ten animals were sacrificed.

C. Operative Techniques

1. General

Prior to each surgical procedure, the animals were fasted overnight. They were transported from the Vivarium to the operating room in cages. One half hour prior to induction of anesthesia, each animal received an intramuscular injection of 2 cc of a potent tranquilizer, acepromazine maleate (Aceprozine, Webster Laboratories Ltd., Toronto).

Anesthesia was induced by inhalation of 5% halothane (Fluothane, Ayerst Lab.) delivered with compressed air at five litres per minute administered via a VMS-Fraser Sweatman anesthetic machine. The anesthesia circuit was semi-closed and incorporated a soda-lime CO_2 absorber. Maintenance was achieved at concentrations of halothane varying between one and two percent at a flow rate of two litres per minute. This system was ideal and provided rapid induction, satisfactory maintenance and muscle relaxation and rapid recovery. No anesthetic complications were encountered at any time during the project.

Following induction of anesthesia, the dogs were placed supine on the operating table and shaved. The skin was then washed

with green soap and prepped with an organic iodine solution (Betadine, Purdue, Frederick Co. Ltd.)

All operative procedures were performed under aseptic conditions including sterilization of instruments and the use of masks and gloves by the operating team.

Intravenous 5% dextrose in saline (500 cc) was administered during intra-abdominal operations and 4 cc of a long-acting penicillin (Derapen, Ayerst Lab.) was given intramuscularly at the end of each procedure.

Following recovery from anesthesia the animals were returned to the Vivarium where food and water were withheld for 48 hours. On the first postoperative day each dog received 500 cc of 5% dextrose in saline by subcutaneous clysis and thereafter diets were advanced back to meat over the course of the next five days.

2. Esophagostomy (One-stage Cervical)

A 5 cm incision was made in the natural skin fold to the left of the trachea, the upper end at the level of the cricoid cartilage. This incision was deepened to expose the sterno-cephalicus muscle which was retracted laterally to enter the loose fascial plane between the trachea medially and the carotid sheath laterally. The cervical esophagus was then easily palpable and a Babcock forcep was used to grasp it. This manoeuvre was facilitated by the presence of a length of 3/8" O.D. tubing passed through the pharynx down the esophagus after induction of anesthesia.

The recurrent laryngeal nerve was identified and dissected free prior to placement of the Babcock. The esophagus containing the tube

was then elevated upwards into the skin incision where 6-8 sutures of 3-0 Mersilene (Ethicon) were used to anchor it to the subcutaneous fascia of the neck.

A 2 cm incision was then made through all layers of the esophagus between the shanks of the Babcock which was then removed.

Completion of the esophagostomy consisted of a continuous suture of 3-0 Dexon (Davis and Geck) joining esophageal mucosa to the margins of the middle third of the skin incision. Two simple absorbable sutures of Dexon were then used to close the remainder of the skin incision.

No problems whatever were encountered with this single-stage procedure. The esophagostomy remained patent and free of infection for the 28 week duration of the project.

3. Highly Selective Vagotomy

Under general anesthesia, the abdomen was opened in the midline from xiphisternum to umbilicus. The falciform ligament was excised to provide a good fascia-to-fascia closure later.

The general technique used was that reported by Johnston and Wilkinson (1970), with several modifications.

No attempt was made to exactly delineate the antral-fundic border. Recently (Johnston *et al* 1973a&b) in the report of the combined results of the Copenhagen/Leeds trials, in which the Copenhagen group used a pH electrode or an intragastric spray of Congo Red dye after stimulation of acid secretion by intravenous pentagastrin to define this border, while the Leeds groups used none. There was no apparent difference in their results so our decision to avoid this

time-delaying procedure appeared to be justified.

The incisura angularis of the stomach was used as the anatomical landmark of this boundary and, following the usually easy identification of the anterior nerve of Latarjet, denervation was begun at this level and proceeded proximally (Fig. 4).

It must be stressed at this time that great care was taken to avoid unnecessary handling of the nerves of Latarjet either by excessive traction or by direct instrumental manipulation of the nerve. Reference to this "no-touch" technique will be made later in the Discussion.

Along the anterior (and posterior) lesser curve of the stomach, the larger gastric nerves usually run in association with vessels to the parietal cell mass (see Chapter II). Consequently, denervation was achieved by isolating these neurovascular bundles and dividing them between medium size stainless steel hemoclips (Weck Surgical, Rexdale, Ont.). Following clearing of these structures, a careful search for minute filamentous nerve branches was made and those found were divided.

In this manner the anterior surface of the lesser curve was denuded down to the outer muscular layer of the stomach. Dissection then proceeded from right-to-left across the gastroesophageal junction and it was in this area that the majority of the small twigs which probably arose directly from the vagal trunks were found.

The stomach was then rotated upwards into the incision and to the right. A large rent was made in the greater omentum to gain access to the posterior surface of the stomach. Again, the posterior

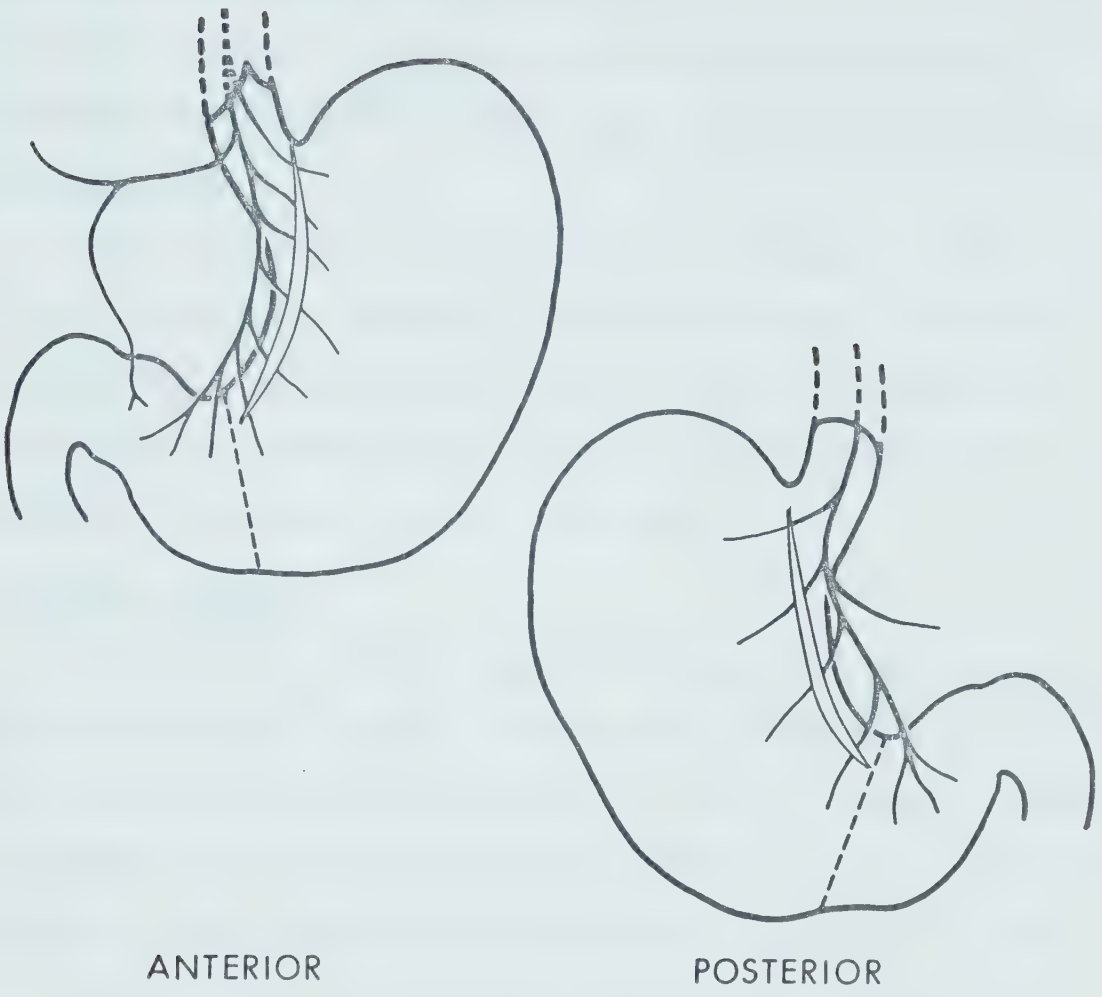

Figure 4 Highly selective vagotomy without pyloroplasty

nerve of Latarjet was usually easily visible and the posterior surface of the lesser curve was denervated in the same manner as the anterior side. Care was taken to avoid damage to the left gastric artery, a point emphasized by Griffith to avoid damage to the celiac division of the posterior trunk.

At the conclusion of this operation, the abdominal cavity was rinsed with copious amounts of saline and suctioned clean of all blood and clots. The abdomen was then closed with interrupted non-absorbable suture (Tevdek, Deknatel) and the skin reapproximated with a subcuticular continuous suture of 3-0 Dexon.

4. Selective Vagotomy

In all cases, selective vagotomy followed a previous highly selective vagotomy so, in theory, this operation should have been performed simply by sectioning the anterior and posterior nerves of Latarjet to the antrum left intact at the previous operation (assuming, of course, the original highly selective procedure had been complete) (Fig. 5).

This, however, was not always possible (witness the failure to denervate three dogs in Stage IIIb). Upon entering the abdomen, encroachment of fatty-fibrous adhesions from the lesser omentum over the previously raw lesser curve were found almost routinely. These adhesions buried the nerves of Latarjet and considerable dissection was necessary in most of the dogs to identify and divide these nerves.

5. Pyloroplasty

In those seven dogs which underwent pyloroplasty, a Heinecke-Mickulicz-type operation was performed after mobilizing the pylorus by

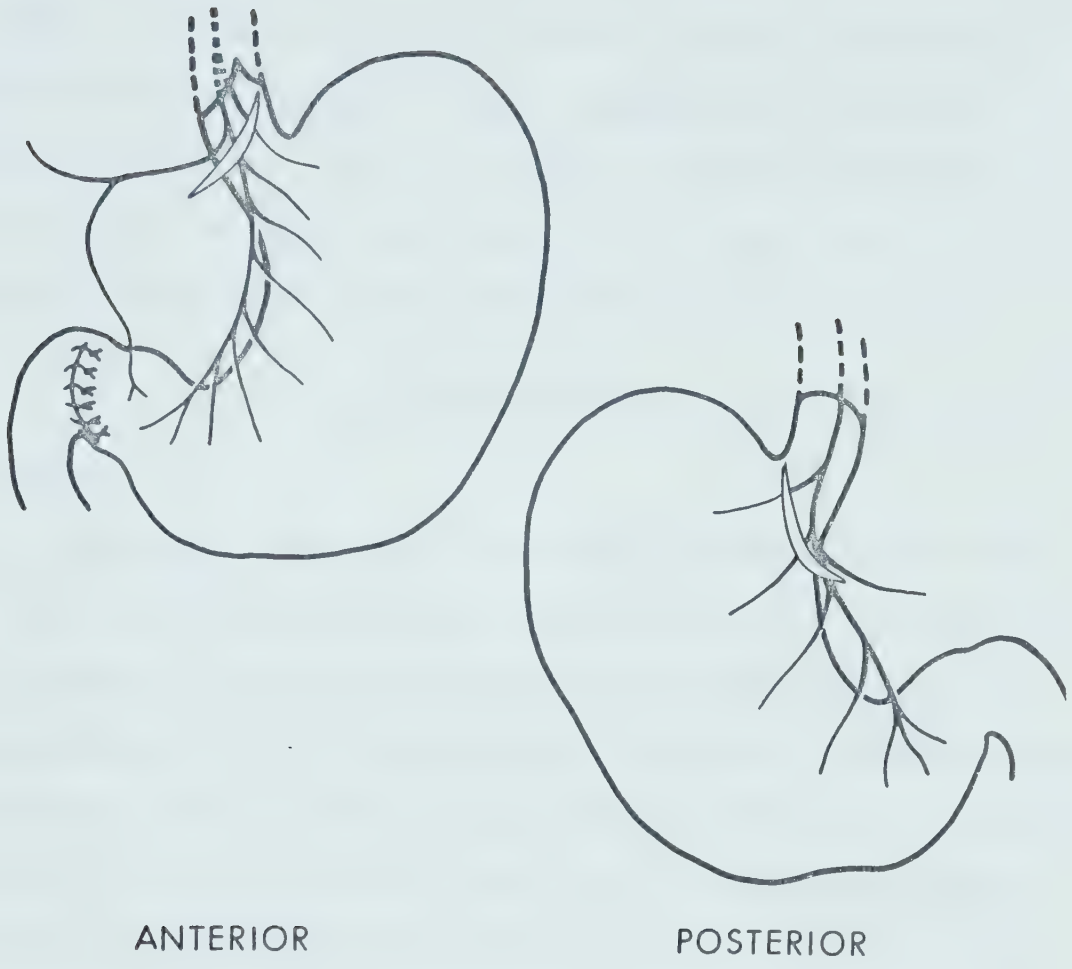

Figure 5 Selective vagotomy with pyloroplasty

division of the congential suspensory ligament and ligation of the prepyloric vessels of Mayo. A through-and-through horizontal incision was then made extending 2 cm on the gastric side and 1 cm on the duodenal side of the pylorus. The gastroduodenal mucosa was then closed vertically as a single layer with 4-0 chromic and the sero-muscular-submucosal layer reapproximated as a second layer, also in a vertical manner, with simple interrupted sutures of 3-0 silk.

D. Testing Techniques

1. General

Twenty-four hours prior to each test procedure, a liquid diet was substituted for the dog's usual meat meal. No food was given on the day of testing. Tests of emptying and secretion were performed via tube-esophagostomy on the whole-stomach preparation, in conscious, non-tranquilized animals, a rather unique feature of this project. It was felt that this preparation would constitute a far more physiological model than animals with numerous pouches of various segments of their gastrointestinal tracts. Each animal was fitted with a 18 Fr. Salem Sump tube (Sherwood Med. Industries, St. Louis) which was positioned under fluoroscopy prior to Stage I (Control) collections and marked at the appropriate length. This mark was left unchanged throughout the project to reduce the error that may have occurred by repeated intubation of different lengths.

On the day of testing, the animals were transported to a special gastric collection room in the basement of the Surgical-Medical Research Institute where they were isolated from external

stimuli. Two or three dogs were tested simultaneously and were isolated from each other by heavy curtains. Each dog was positioned in a wooden Pavlov frame in which it had been conditioned to stand, and was supported by a specially designed harness. Tubes were positioned and held in place by clipping to an adhesive-tape collar.

All intravenous infusions and medications were administered via a 20 gauge plastic intravenous cannula (Medicut, Argyle) installed prior to the beginning of each test.

Following completion of each test, the dogs were returned to the vivarium and fed.

2. Gastric Emptying

Gastric emptying rate was determined using a modification of Hunt's phenol red technique (Hunt and Knox, 1962) in which phenol red (a,a-bis (p-Hydroxy phenol)-a-hydroxy-o-toluene y Sultone), a dye which is neither absorbed in, nor secreted by the stomach, is administered, left in the stomach a known length of time and then aspirated. The rate of emptying was determined by measuring the amount of dye recovered and expressing this amount as a function of time.

The dye was freshly prepared each test morning in a dextrose solution [48.7 grams dextrose (Fisher Chemical Co.) plus 6 ml of 0.1% phenol red solution (Fisher Chemical Co.) per litre of water; pH adjusted to 7.00 with 2N HCl; osmolarity 310 mOsm/litre], and warmed in a water bath to 37°C. The test animal's stomach was then aspirated by high (20 inches H_2O) suction until empty. 300 cc of the phenol red/dextrose solution was administered via gravity through the tube esophagostomy. When all the dye had entered the stomach, a clock

was started.

Six tests were conducted on each animal on a single test day. Dye was left in the stomach for five minutes during the first test, and thereafter the length of each test was increased in five minute intervals to a maximum of 30 minutes. The dog was allowed a 10 minute rest between each of the six tests.

Following the initial administration, the dye was mixed by syringe with the residual gastric contents for 45 seconds (by the clock), a time shown to be enough to allow thorough mixing (George, 1968), and a 10 cc sample was withdrawn and marked "$T_xV_1C_1$", where x was the number of the test (i.e., 1,2,3,4,5, or 6). Analysis of this sample ultimately provided the starting volume and concentration (i.e. the starting amount).

At the end of the prescribed time period, the stomach was immediately and rapidly aspirated of the residual dye which was placed in a second container marked "T_x V_2C_2". Analysis of this sample provided most of the recovered amount.

Finally, a 50 cc volume of warm tap water was administered by syringe down the tube, aspirated, reinjected and finally completely aspirated into a third container marked "$T_xV_3C_3$". This "wash" recovered any residual dye in the stomach, and when added to the second sample, provided the total amount of dye recovered.

The clock was then started for the 10 minute rest and the entire process was repeated. The six tests were always performed in sequence (i.e. 5 min, 10 min, 15 min, etc), and were not randomized.

3. Pentagastrin-Stimulated Secretion of Acid and Pepsin

Following positioning of the dog and establishment of the intravenous line, 500 cc of distilled water was administered via gravity through the tube and aspirated to wash the stomach prior to commencing the test.

Each pentagastrin test lasted six hours. During the first and the sixth hour, the animals received 100 cc of 5% dextrose in saline intravenously to provide a baseline of secretion for subsequent comparison with maximal levels of stimulated secretion. During the second to the fifth hour, an intravenous pentagastrin solution [340 µg pentagastrin (Peptavlon AY-6608, Ayerst) mashed with 1-2 drops of a solution consisting of 95 ml 5% dextrose in saline and 5 ml of KCl solution containing 10 mEq K^+, the final volume made up to 100 ml, final concentration 3.33 µg pentagastrin/ml] was administered by infusion pump (Harvard) through a 100 cc syringe at pump speeds sufficient to deliver concentrations varying from 0.75 to 7.43 µg/kg/hr. These speeds and concentrations were chosen to provide a dose-response curve based on doubling the dose of pentagastrin in hourly infusions.

Gastric juice was collected by continuous low (3-5 cm H_2O) suction in six one-hour samples.

During the first two stages of the project, serum glucose and electrolytes were studied to ensure no changes in secretion could be ascribed to changes in blood chemistry. This was abandoned in the latter half of the work when significant changes in those parameters were not found.

At the end of each test, the animals were returned to the

Vivarium and fed.

4. Insulin Tests

Ross and Kay's (1964) modification of the Hollander test was used as a measure of completeness of vagotomy.

After positioning in the Pavlov frames and installation of an intravenous cannula, 2 cc of blood were drawn for a fasting determination of blood glucose. The cannula was then capped and left in place for subsequent insulin injection and blood sampling.

The fasting gastric juice was then aspirated. Continuous low suction was maintained throughout each insulin test.

Two 15-minute basal collections were then performed prior to administration of Toronto insulin (Connaught) in doses varying from 0.3 to 0.5 units/kg. The higher dosage was used in the early stages but abandoned in favor of the lower one after one dog had a grand mal seizure on two occasions.

Following administration of insulin, gastric secretion was collected in 15-minute aliquots for a period of two hours.

Forty-five minutes after insulin injection, another 2 cc sample of venous blood was withdrawn through the cannula for glucose determination. A final 2 cc sample was withdrawn at the conclusion of each test.

Immediately upon completion, the dogs were returned to the Vivarium and fed.

5. Pre-terminal Studies of Completeness of Vagotomy

Major R.E. Cole (1972) recently described a simple test to

visually determine the extent of residual vagal innervation to the parietal cell area of the stomach after vagotomy. He even advocates this procedure for routine intra-operative use.

Following induction of anesthesia, the abdomen was opened and a large gastrotomy performed along the upper part of the greater curvature of the stomach. The mucosal surface was wiped clean of mucous and debris and a fresh, damp sponge was carefully placed to cover the entire mucosal surface of the parietal cell mass. The pylorus was packed with a 4x4 gauze sponge to prevent bile reflux.

2-deoxy-D-glucose (Fisher Chemical Co.), 50 mg/kg was then injected intravenously. This compound is believed to cause a cerebral cytoglucopenia, i.e. a relative hypoglycemia, and thereby causes profound stimulation of the hypothalamic vagal centers.

Exactly 10 minutes after administration of the 2-deoxy-D-glucose, 10 cc of a 1% solution of neutral red (Fisher Chemical Co.) dye was given intravenously. This dye has the unique property of being secreted by parietal cells only under vagal stimulation (Pritchard *et al*, 1968). If areas of residual vagal innervation are present, a characteristic pink color appears through the dampened sponge from the innervated area beneath it.

This simple test was performed on all the animals under anesthesia prior to sacrifice.

E. Biochemical Analysis of Samples

1. Phenol Red Emptying Tests

The volume of each sample was first carefully measured.

Then one ml of each sample was added to 5 ml of phosphate buffer and the volume adjusted to 25 ml with water. A small aliquot of the final solution was read in a Unicam SP 1800 spectrophotometer against a blank of phosphate buffer.

The results were expressed in millilitres in terms of volume and as milligrams per litre in terms of phenol red concentration.

2. Secretion Tests

a. Acid

The volume of each sample of gastric juice obtained from either the pentagastrin-stimulation or the insulin tests was measured.

A one ml aliquot of each sample was then titrated to pH 7.00 with 0.1 N NaOH using a Radiometer Model TTT1 automatic titrator. Total $[H^+]$ titratable to pH 7.00 was measured and expressed initially in milliequivalents per litre. Secretion in milliequivalents per hour was then calculated.

b. Pepsin

In the case of pentagastrin-stimulated secretion, pepsin concentration was measured on the six-hour pooled specimens after acid analysis. The enzyme was measured according to Aitken's method (1954). In brief, a one ml sample of the pooled gastric juice was diluted to 10 ml with 0.1 N HCl and 1.0 ml of this solution was incubated with a hemoglobin solution of 37°C for 10 minutes. Thereafter, 10 ml of 0.3 N Trichloroacetic acid were added and the precipitated proteins were filtered off. The amount of tyrosine-like substances liberated (by pepsin) during incubation were measured cholorimetrically using

Folin-Coicalteau reagent (Fisher Chemical Co.) against a standard of known tyrosine in a Beckman DU spectrophotometer.

The final concentration of pepsin was expressed in milligrams per millilitre of gastric juice, and the actual amount of pepsin secreted was then calculated.

3. Blood Chemistry Tests

a. Glucose

Blood glucose was determined using a Sigma Kit #510 (Sigma Chemical Co.). This is an enzymatic, colorimetric determination using a spectrophotometer. Blood glucose concentration so determined is expressed as milligrams per 100 millilitres of whole blood (mg%).

b. Electrolytes

Sodium and potassium ion concentration in gastric juice and serum were measured by emission flame photometry on an I.L. Model 143 Flame Photometer using lithium as an internal standard. Results were expressed as milliequivalents per litre.

Chloride ion determination was measured by the potentiometer method using a Buchler-Cotlove Chloridometer. Results were also expressed in milliequivalents per litre.

F. Analysis of Results

1. Phenol Red Emptying Tests

The rate of gastric emptying of this liquid test meal is determined by the ratio of the amount administered and the amount recovered.

The amount of dye in the stomach at the beginning of each

test time period is given by:

(1) $18{,}000 - (V_1 \times C_1)$

where 18,000 is the amount of dye actually given to the animal (300 cc x 600 mg/L) and $(V_1 \times C_1)$ is the amount of dye removed in the first sample and is therefore not actually included in that quantity of dye which ultimately either passes through the pylorus or remains in the stomach at the end of the test period.

The amount of dye recovered is given by the formula:

(2) $(V_2 \times C_2) + (V_3 \times C_3)$

In reviewing Hunt's original data Hopkins (1966) demonstrated that the rate of gastric emptying of the dye was more closely proportional to the square root of the amount of dye remaining in the stomach than in the logarithm of the volume remaining, as suggested by Hunt. That is

(3) Rate of emptying of phenol red $\propto \sqrt{\frac{\text{amount given}}{\text{amount recovered}}}$

By combining these three formulas:

(4) Rate of emptying of phenol red $\propto \sqrt{\frac{18{,}000 - (V_1 \times C_1)}{(V_2 \times C_2) + (V_3 \times C_3)}}$

Thus the rate of emptying is expressed as a square root function against time.

Two tests of phenol red emptying were performed on each dog after each stage.

Initially these results were calculated on a simple desk calculator. This operation proved tedious and time-consuming. As

a result, an APL program was written and the raw data was presented to the University of Alberta IBM 360/67 computer which handled all the calculations (Fig. 6), as well as the statistical computations, in considerably less time.

Emptying rates from stage-to-stage were compared to the use of a linear regression technique (Sokal and Rohlf, 1969). The slope of the best-fit straight line were determined by the least-squares method and these slopes were then compared from stage-to-stage using the paired t test (Sokal and Rohlf, 1969).

2. Secretion Tests

a. Acid

Hydrochloric acid secretion was expressed as the number of milliequivalents of acid per volume of sample, i.e. the actual number of milliequivalents secreted. Data for acid and pepsin secretion were obtained as two replicates for each animal after each of the various operations. Because of the inherent variability of the control results it was considered inappropriate to test the distribution of the differences via the paired t test. Instead it was more reasonable to test whether there had been an increase or decrease in gastric acid secretion following each stage of the project. Consequently the means of the data to be compared were classified as "increased" or "decreased" and the probability of this distribution was assessed by the chi-squared test (Sokal and Rohlf, 1969).

b. Pepsin

Mean values of pepsin secretion were compared by the same method

```
      ∇NEMESIS[⎕]∇
    ∇ R←NEMESIS;T;X;VP;C1;V2;C2;V3;C3;MAT
[1]   T←(5×⍳6),X←⍳0
[2]   'ENTER V'''
[3]   VP←⎕
[4]   'ENTER C1'
[5]   VP←C1×18000-VP×C1←⎕
[6]   'ENTER V2'
[7]   V2←⎕
[8]   'ENTER C2'
[9]   V2←V2×⎕
[10]  'ENTER V3'
[11]  V3←⎕
[12]  'ENTER C3'
[13]  X←X,(V2+V3×⎕)÷VP
[14]  'MORE DATA?'
[15]  →('Y'=1↑⍞)/2
[16]  →(6≠ρX)/LABEL1
[17]  'RESIDUAL AMOUNTS ARE ';3 RND X
[18]  'AT TIMES ';T
[19]  'ROOTS OF RESIDUAL AMOUNTS ARE ';3 RND X*0.5
[20]  60 80 PLOT⍉(2 6)ρT,X*0.5
[21]  →0
[22] LABEL1:'TABLE OF TIMES AND RESIDUAL AMOUNTS'
[23]  ⎕←3 RND MAT←((1+(ρX)÷6),6)ρT,X
[24]  ''
[25]  'TIMES AND ROOTS OF RESIDUAL AMOUNTS'
[26]  ⎕←3 RND MAT←((1 6)ρMAT[1;]),[1] R←((1 0)↓MAT)*0.5
[27]  ''
[28]  'MEAN,SD AND SE OF ABOVE '
[29]  ⎕←3 RND MAT←SDD(1 0)↓MAT
[30]  R←R,[1] MAT
[31]  ''
[32]  'DOG NUMBERS IN THIS EXPERIMENT WERE?'
[33]  VP←⍞
[34]  60 80 PLOT⍉(2 6)ρT,MAT[1;]
    ∇


      ∇REG[⎕]∇
    ∇ REG;X;Y
[1]   X← 5 10 15 20 25 30
[2]   →(0=ρY←⍞)/0
[3]   'SLOPE IS ';(X LSQPLOT Y)[1]
[4]   →2
    ∇
```

Figure 6 The "Nemesis" program for calculation of phenol red emptying.

as acid secretion data.

In all cases of emptying or secretion a P value of 0.05 or less was considered statistically significant.

3. Insulin Tests

As previously mentioned, the criteria of Ross and Kay (1964) were used to evaluate the response to insulin after each stage of surgery. According to these criteria, a rise in total acid secretion of greater than 20 mEq/L over the mean basal value is a positive response. If the basal secretion were anacid, a rise greater than 10 mEq/l. was considered positive. The maximal acid secretion is regarded as the mean of the two highest values which occurred consecutively. The mean basal value is the arithmetical average of the acid secretion during the two basal 15-minute collections before insulin administration.

The positive responses are further divided into early positive (in which the mean maximal response is reached in the first hour after insulin) and late positive (maximum value occurring in the second hour). This division is of clinical significance in that an early response is considered to represent incomplete inadequate vagotomy and the patient is "at risk" to ulcer recurrence. A late positive response is interpreted as an incomplete but probably adequate vagal denervation.

Only one insulin test was performed on each dog after each stage of the project.

4. 2-deoxy-D-glucose Studies of Completeness of Vagotomy

This test, although performed objectively, may only be evaluated subjectively by a description of the estimated area of the patches of dye seen representing residual vagal innervation.

CHAPTER IV

RESULTS

The ten test animals remained in good health throughout the four stages of the project despite a rigorous testing schedule and three major intra-abdominal procedures each. Average weight loss over the duration of the investigation was 4.7 kg. Two animals had post-operative wound dehiscence after Stage I surgery; both were repaired without difficulty or sequelae. No other major complication or illnesses occurred.

A. Changes Observed in Gastric Emptying of Phenol Red

The modified phenol red solution as described was tolerated without apparent nausea and without a single instance of vomiting in all the animals. In this regard, it would subjectively appear to be a reliable tool to investigate the rate of gastric emptying of a liquid test meal.

The parameters chosen for this study (volume, concentration and time) were, in retrospect, adequate and the test was sensitive enough to display stage-by-stage changes in the rate of gastric emptying.

Using the linear regression technique for statistical analysis, all the control data were fitted by a straight line without significant error. In addition, in all cases except selective vagotomy with pyloroplasty, the values obtained after operation could also be fitted by a

straight line without significant error.

1. The Effect of Highly Selective Vagotomy

The salient cahnges observed were:

(1) Highly selective vagotomy produced no significant change in the rate of gastric emptying of the dye solution compared to preoperative values (Fig. 7a),

(2) The addition of pyloroplasty to highly selective vagotomy likewise produced no significant changed (Fig. 7b).

2. The Effect of Selective Vagotomy

(1) Division of the nerves of Latarjet to the antrum (following highly selective vagotomy) produced slower emptying than control values (Fig. 7c).

(2) Emptying following selective vagotomy was slower than after highly selective vagotomy (Fig. 7e).

(3) In the case of selective vagotomy with pyloroplasty, the data differed significantly from linearity. Reference to figures 7d, 7f and 7g discloses that the anomalous point is the one at five minutes since, if this point is omitted, regression shows the data adequately fit a straight line.

This suggests that after selective vagotomy with pyloroplasty, the emptying rate during the first five minutes of the initial challenge of the stomach by the test meal is significantly faster than control, highly selective vagotomy or highly selective vagotomy with pyloroplasty. It would appear from the results of the animals that had undergone selective vagotomy with pyloroplasty that there was actually more dye

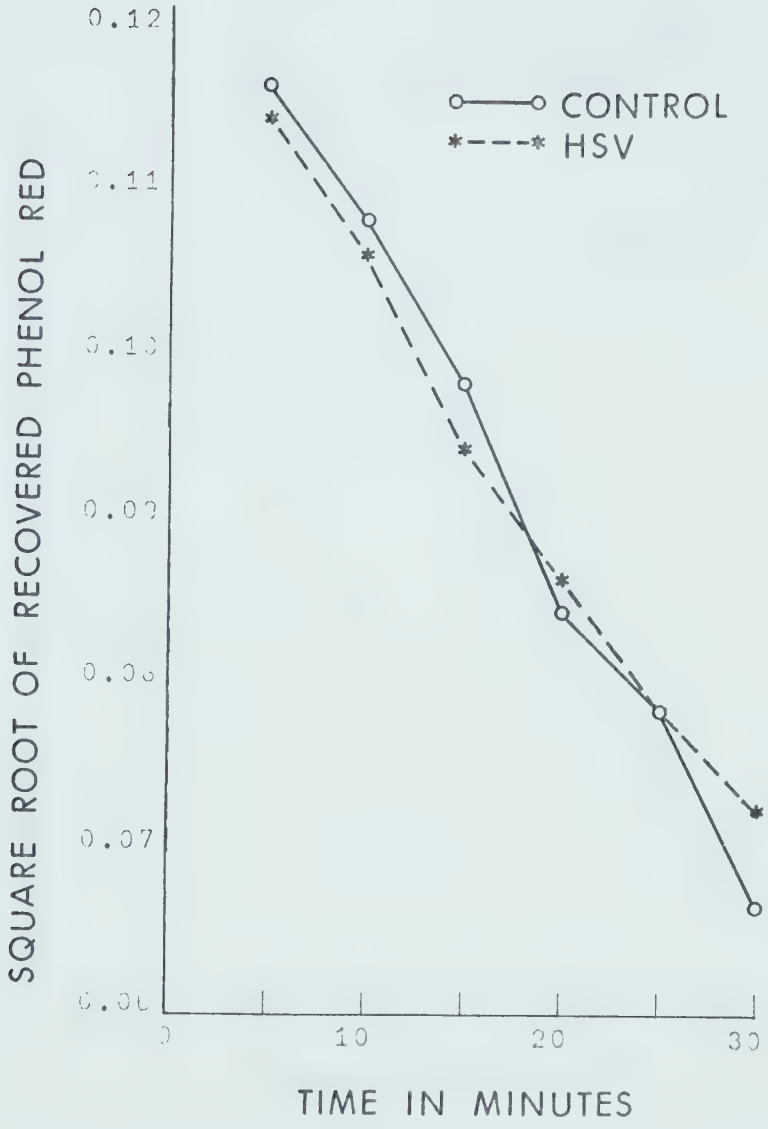

Figure 7a The gastric emptying of phenol red: Comparison of highly selective vagotomy to control.

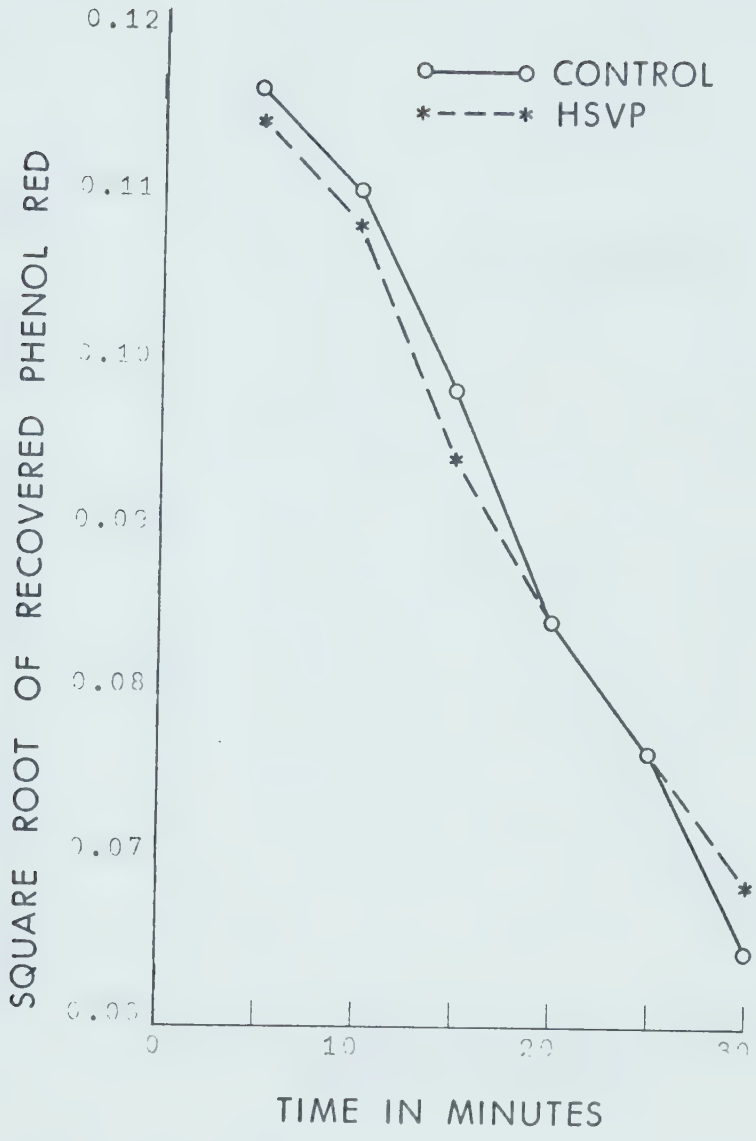

Figure 7b The gastric emptying of phenol red: Comparison of highly selective vagotomy with pyloroplasty to control.

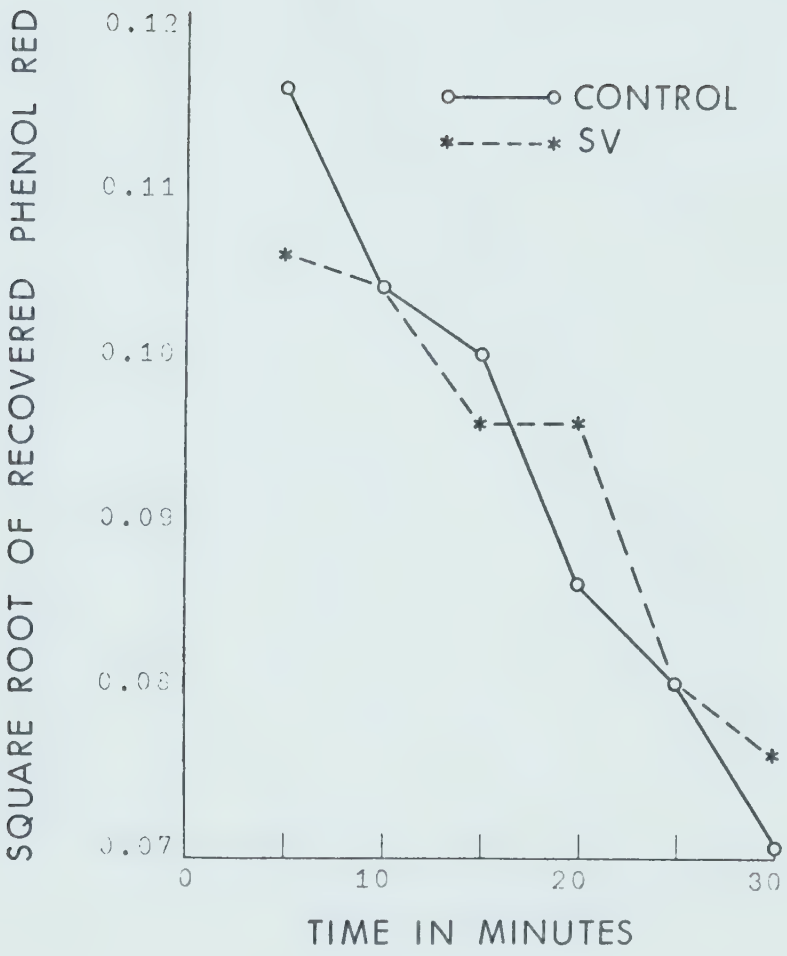

Figure 7c The gastric emptying of phenol red: Comparison of selective vagotomy to control.

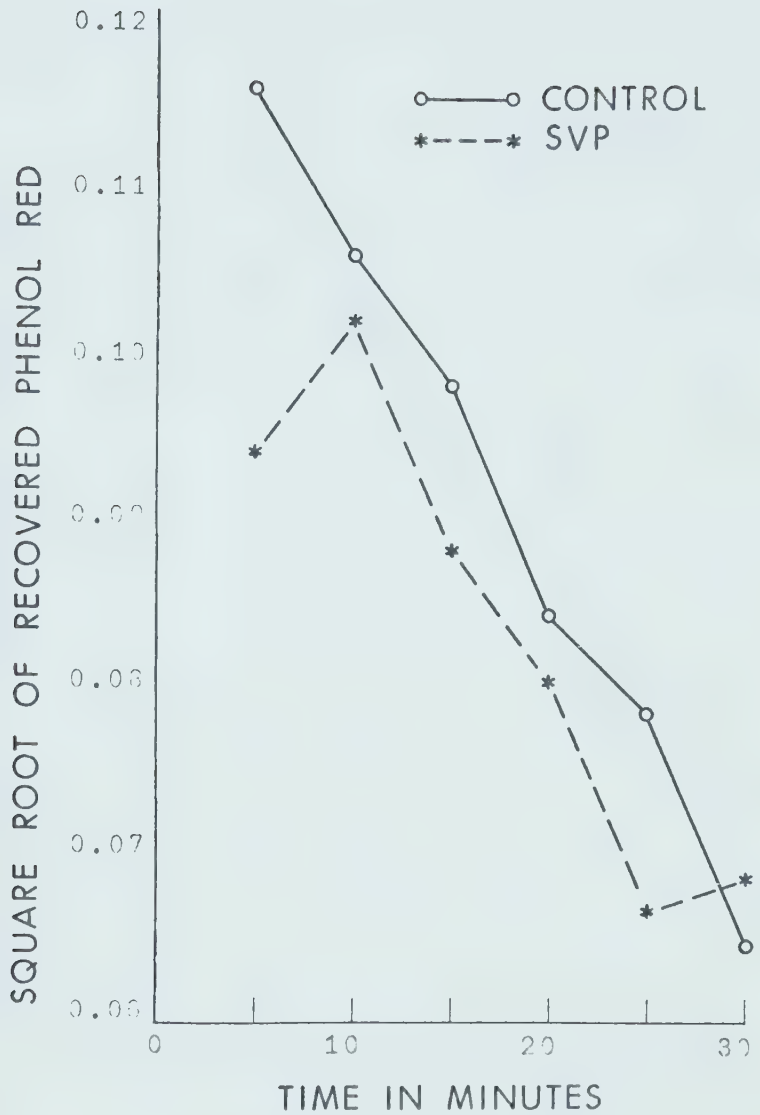

Figure 7d The gastric emptying of phenol red: Comparison of selective vagotomy with pyloroplasty to control.

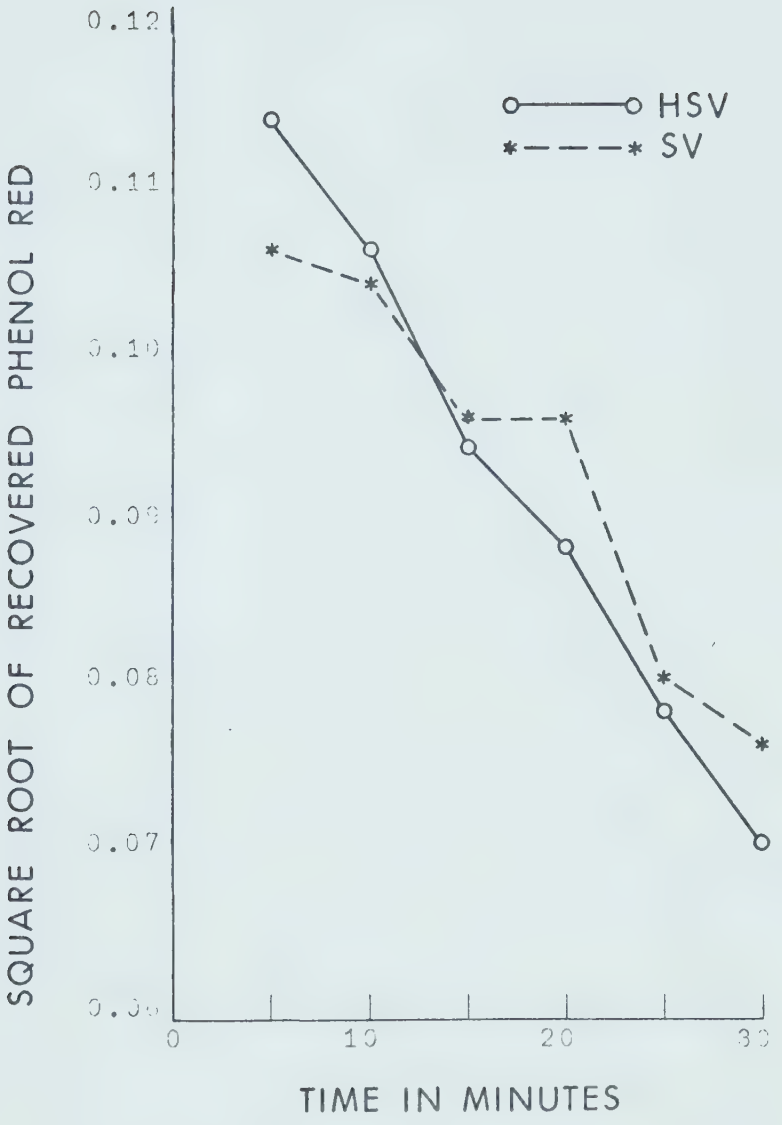

Figure 7e The gastric emptying of phenol red: Comparison of selective vagotomy to highly selective vagotomy.

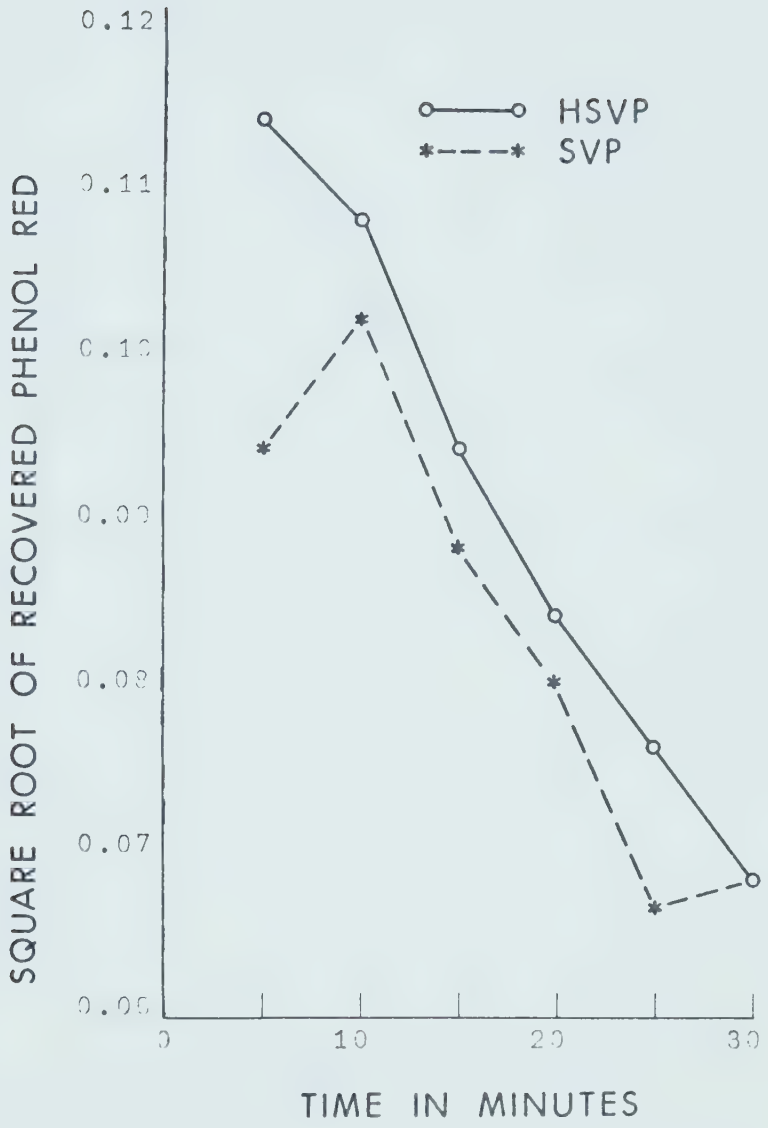

Figure 7f The gastric emptying of phenol red: Comparison of selective vagotomy with pyloroplasty to highly selective vagotomy with pyloroplasty.

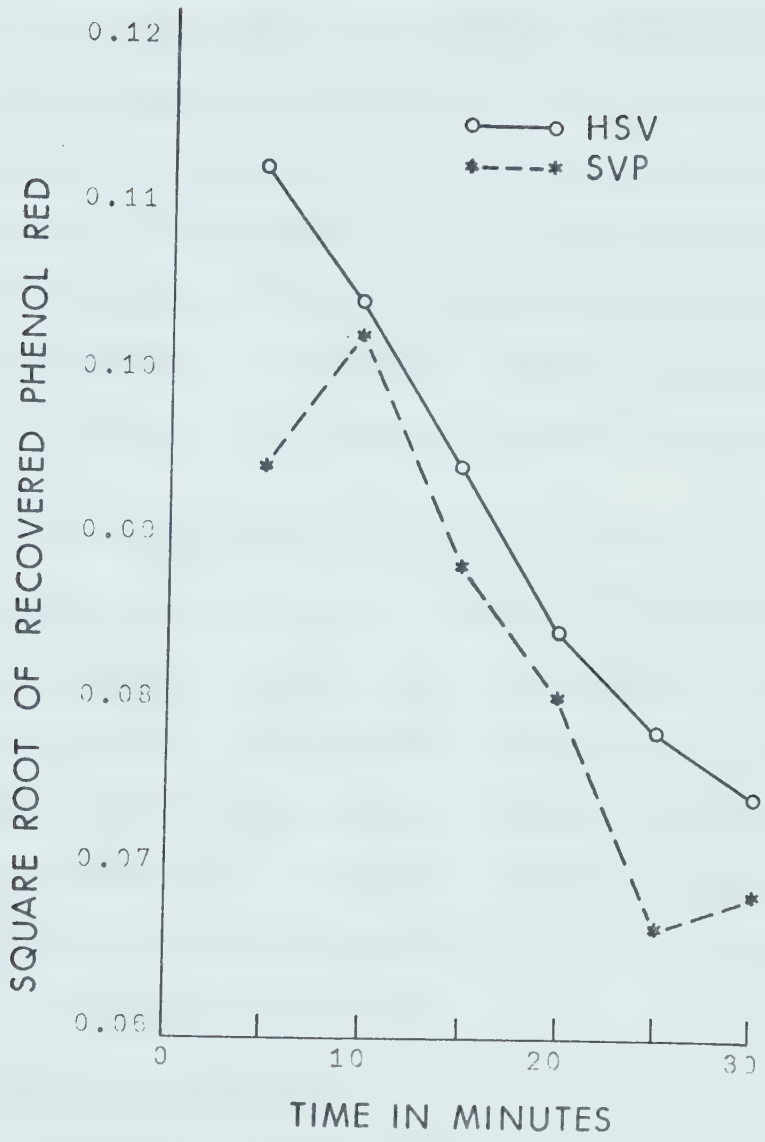

Figure 7g The gastric emptying of phenol red: Comparison of selective vagotomy with pyloroplasty to highly selective vagotomy.

in the stomach at ten minutes than at five. It is possible that this apparently extraordinary finding is an artifact created by the sequential sampling of the liquid meals (see Methods). These results may be interpreted by supposing that the initial challenge with the test meal following selective vagotomy with pyloroplasty provokes rapid gastric emptying which is not reproduced by later administrations. This observation is worthy of further investigation since it cannot be determined from these results whether the initial rapid emptying is followed by a slower rate or whether the rate later reverts to normal.

B. Changes Observed in Gastric Secretion of Acid and Pepsin

As mentioned previously in Chapter III, studies of serum electrolytes and blood glucose levels at the beginning and end of each 6-hour experiment were performed during Stages I and II. No significant change in these parameters occurred, thereby establishing that the observed changes in secretion were due to pentagastrin stimulation and not to hypoglycemia or to changes in serum sodium, potassium or chloride concentration.

1. Changes in Acid Secretion

a. Basal (Resting) Acid Output (Table I)

(1) Highly selective vagotomy produced no significant change in basal acid secretion compared to control values.

(2) Addition of pyloroplasty to highly selective vagotomy similarly produced no change in basal secretion compared to normal.

(3) Selective vagotomy caused a profound 92.8% decrease in

TABLE I

SECRETION STUDIES

Mean Basal Acid Output

mEq HCl/hour

Dog No.	Control	HSV*	HSVP¶	SV†	SVP§
J-1436	0.40	3.24	0.63	-	0.02
K-181	0.01	0.11	-	0.01	0.02
K-413	0.01	0.18	2.58	-	0.01
K-509	0.79	1.69	0.72	-	0.01
K-514	3.90	7.58	-	0.23	-
K-554	0.01	0.84	-	0.01	0.01
K-627	1.38	4.43	-	0.38	-
K-786	1.15	0.25	0.16	-	0.01
K-804	1.41	1.27	3.04	-	0.01
K-834	7.62	7.48	-	0.01	-

*HSV - highly selective vagotomy
¶HSVP - highly selective vagotomy & pyloroplasty
†SV - selective vagotomy
§SVP - selective vagotomy & pyloroplasty

resting secretion compared to normal and a 95.6% decrease when compared to highly selective vagotomy.

(4) Selective vagotomy with pyloroplasty produced similar results to selective vagotomy alone.

b. Pentagastrin-Stimulated Maximal Acid Output

(1) Maximal acid secretion under pentagastrin stimulation was not altered significantly with reference to normal by either highly selective vagotomy or highly selective vagotomy with pyloroplasty (Table II).

(2) Selective vagotomy, in contrast, produced a 43.7% decrease in this parameter. Results after selective vagotomy with pyloroplasty were similar.

c. Changes in Pepsin Secretion

(1) Neither highly selective vagotomy nor the addition of pyloroplasty to it produced significant changes in the secretion of this enzyme (Table III).

(2) In a manner similar to its effect on acid secretion, selective vagotomy caused a profound decrease in secretion. Compared to control values, selective vagotomy decreased pepsin secretion 84.7%; compared to highly selective vagotomy, a decrease of 82.8% was noted.

(3) Addition of pyloroplasty to selective vagotomy produced essentially similar results to those in (2) above.

d. Observations on the Insulin Test

It was this test that produced by far the most confusing and

TABLE II

SECRETION STUDIES

Mean Pentagastrin-Stimulated Maximal Acid Output

mEq HCl/hour

Dog No.	Control	HSV*	HSVP¶	SV†	SVP§
J-1436	15.22	21.02	12.17	-	15.69
K-181	18.55	15.17	-	6.90	8.00
K-413	8.39	24.22	24.29	-	10.11
K-509	20.91	19.69	17.99	-	10.00
K-514	29.93	30.40	-	14.00	-
K-554	11.07	22.39	-	8.40	6.58
K-627	4.55	13.16	-	5.29	-
K-786	21.91	12.67	9.88	-	9.79
K-804	9.73	19.45	10.36	-	7.38
K-834	20.34	17.99	-	10.69	-

*HSV - highly selective vagotomy
¶HSVP - highly selective vagotomy & pyloroplasty
†SV - selective vagotomy
§SVP - selective vagotomy & pyloroplasty

TABLE III

SECRETION STUDIES

Mean Pepsin Secretion

Gms/6 hours

Dog No.	Control	HSV*	HSVP¶	SV†	SVP§
J-1436	1.06	1.31	1.06	-	0.54
K-181	1.16	0.63	-	0.25	0.12
K-413	0.64	1.39	1.44	-	0.31
K-509	1.20	0.77	1.23	-	0.10
K-514	2.75	2.82	-	0.16	-
K-554	1.23	2.54	-	0.19	0.10
K-627	2.62	3.54	-	0.70	-
K-786	4.19	1.07	0.92	-	0.31
K-804	3.29	1.76	2.56	-	0.33
K-834	2.87	2.84	-	0.35	-

*HSV - highly selective vagotomy
¶HSVP - highly selective vagotomy & pyloroplasty
†SV - selective vagotomy
§SVP - selective vagotomy & pyloroplasty

frustrating results throughout the project. With reference to Table IV, it may be observed that the insulin test in three normal, preoperative animals was late positive by Ross and Kay's criteria. Moreover, the author was unable to demonstrate a single negative insulin test regardless of the extent of vagal section in any animal and in spite of proved hypoglycemia in every test performed.

Because of the confusion created by these "qualitative" results, a quantitative analysis of the acid secretion in response to insulin stimulation at each stage was performed.

e. Changes in Hourly Basal Acid Output Prior to Insulin Injection

Statistical analysis of these results (Table V) indicated that no operative treatment except the addition of pyloroplasty to highly selective vagotomy produced a significant change in this parameter.

f. Changes in Total Acid Output Following Insulin Injection (Table VI)

The only finding of significance in this study was that 2-hour insulin stimulated acid secretion after selective vagotomy with pyloroplasty was lower than that after highly selective vagotomy.

g. Terminal Test of Completeness of Vagotomy

The results of this qualitative test and a comparison of each animal's final insulin test is shown in Table VII. Obviously no direct correlation can be made - one animal (K-627), in which only 2% of less of the parietal cell mucosa stained suggestive of residual innervation, continued to demonstrate an early positive insulin test while another animal (K-786), in which one-quarter of the mucosa stained, showed a late positive response.

TABLE IV

THE INSULIN TEST

(According to Ross and Kay's Criteria)

All Responses POSITIVE

Dog No.	Control	HSV*	HSVP¶	SV†	SVP§
J-1436	early	late	late	-	late
K-181	late	early	-	late	late
K-413	early	early	late	-	early
K-509	late	late	late	-	late
K-514	late	late	-	late	-
K-554	early	late	-	late	late
K-627	early	early	-	early	-
K-786	early	early	late	-	late
K-804	early	early	late	-	early
K-834	early	late	-	late	-

*HSV - highly selective vagotomy
¶HSVP - highly selective vagotomy & pyloroplasty
†SV - selective vagotomy
§SVP - selective vagotomy & pyloroplasty

TABLE V

THE INSULIN TEST

Basal Acid Output Prior to Injection of Insulin

mEq HCl/hour

Dog No.	Control	HSV*	HSVP¶	SV†	SVP§
J-1436	0.70	1.04	0.00	-	0.00
K-181	0.08	0.00	-	0.06	0.10
K-413	0.00	0.00	0.00	-	0.00
K-509	0.00	0.08	0.02	-	0.00
K-514	0.00	1.02	-	1.48	-
K-554	0.30	0.00	-	0.28	0.26
K-627	0.00	3.82	-	0.48	-
K-786	0.14	0.46	0.02	-	0.32
K-804	0.00	5.32	0.52	-	0.04
K-834	11.54	11.90	-	0.02	-

*HSV - highly selective vagotomy
¶HSVP - highly selective vagotomy & pyloroplasty
†SV - selective vagotomy
§SVP - selective vagotomy & pyloroplasty

TABLE VI

THE INSULIN TEST

Total Acid Output Following Insulin Injection

mEq HCl/2 hours

Dog No.	Control	HSV*	HSVP¶	SV†	SVP§
J-1436	9.99	14.93	33.48	-	8.54
K-181	22.16	2.98	-	0.71	1.03
K-413	0.80	7.57	2.56	-	1.06
K-509	19.18	33.50	24.01	-	3.32
K-514	51.89	20.55	-	2.48	-
K-554	34.47	25.95	-	0.68	2.92
K-627	10.20	16.63	-	20.63	-
K-786	5.06	2.37	15.85	-	1.70
K-804	1.96	10.30	9.64	-	7.33
K-834	23.18	10.45	-	3.36	-

*HSV - highly selective vagotomy
¶HSVP - highly selective vagotomy & pyloroplasty
†SV - selective vagotomy
§SVP - selective vagotomy & pyloroplasty

TABLE VII

The 2-deoxy-D-glucose/Neutral Red Test of Completeness of Vagotomy with Comparison to the Final Insulin Test

Dog No.	Estimate of Area of Staining as Percentage of Entire Parietal-Cell Mucosal Surface Area	Final Insulin Test (according to Ross and Kay's Criteria
J-1436	<2%	Late positive
K-181	10-15%	Late positive
K-413	5%	Early positive
K-509	2%	Late positive
K-514	5%	Late positive
K-554	<2%	Late positive
K-627	<2%	Early positive
K-786	25%	Late positive
K-804	5%	Early positive
K-834	5-10%	Late positive

B. Summary of Results

Highly selective vagotomy produced no significant changes in either emptying or secretion of acid or pepsin. Selective vagotomy alone produces slower emptying than normal or highly selective vagotomy and, as well, causes significant reduction in both basal and pentagastrin stimulated maximal acid secretion and pepsin output. Selective vagotomy with pyloroplasty produces changes similar to selective vagotomy alone in acid and pepsin secretion but, in the case of the acid results, those changes lie just outside the bounds of statistical significance. The changes in pepsin secretion after selective vagotomy with pyloroplasty are significant. Addition of pyloroplasty to selective vagotomy produces an emptying pattern characterized by an initial rapid phase of emptying on the first exposure to the test meal. On repeated testing, the emptying pattern after selective vagotomy with pyloroplasty assumes a normal configuration.

The insulin test and the 2-deoxy-D-glucose/neutral red test of completeness produced ambiguous results.

CHAPTER V

DISCUSSION

A. Gastric Emptying of Phenol Red

1. After Highly Selective Vagotomy

That no significant change occurred in emptying after highly selective vagotomy confirms the reports by Amdrup and Griffith (1969), Interone *et al* (1971) and Kragelund *et al* (1972). Even more specifically, it confirms the recent report by Clarke and Williams (1972) that highly selective vagotomy preserves the emptying of liquid meals most near-normal.

If the initial highly selective vagotomies in our animals were complete, it may be assumed that preservation of antral innervation is all-important in preserving normal emptying and, incidentally, that the direct gastric branches of the vagus appear to have no control whatsoever on the rate of gastric emptying.

It was surprising to find that addition of pyloroplasty to highly selective vagotomy caused no appreciable increase in the rate of emptying and that the combined operation produced results that were also no different from normal. Even though the pyloroplasty performed was small and "physiological", it was large enough to cause obvious changes later in the project. Precisely why it caused no change in emptying after highly selective vagotomy is not clear but as part of a general rule it may be noted that in the presence

of intact antral innervation, the physical size of the pylorus, (provided it is at least normal) is unimportant.

The clinical argument concerning the necessity for routine complementary drainage in association with highly selective vagotomy would now appear to be solely academic, at least in terms of emptying of liquids through a non-stenosed pylorus, since both operations yielded results not significantly different from normal.

2. After Selective Vagotomy

Selective vagotomy alone resulted in gastric emptying which was slower than normal, a finding which corroborates the experimental work of Shiina and Griffith (1969). The cause of this inertia was not specifically investigated but must be related to antral denervation since emptying was previously normal with that same innervation intact. The observed results argue against Burge's trial of selective vagotomy without drainage (Burge *et al*, 1969).

The phenol red emptying results after selective vagotomy with pyloroplasty were also similar to those reported by Clarke and Williams (1972). Using a similar technique, they also reported an initial rapid rate of emptying which thereafter approached normal. It is quite conceivable that this initial rapid phase of emptying accounts for the high incidence of the "dumping" syndrome which follows this operation.

Why should these changes associated with pyloroplasty prevail after selective and not after highly selective denervation? Any contribution made by direct pyloric innervation may be ruled out since the pyloric branches of the anterior vagal system should have been

preserved intact by either operation. The most likely explanation must evolve from a change in antral peristalsis since the only basic difference in the two procedures was the presence or absence of antral innervation.

In an intensive electrical and mechanical study of the motor characteristics of the canine gastroduodenal junction, Carlson *et al* (1966) reported on one specific type of antral contraction. Termed Type II, this contraction began in the gastric cardia and progressed in a peristaltic manner toward the angle of the stomach where the contraction deepened, propelling gastric content before it. Upon reaching the terminal 3-4 cm of the antrum, the entire terminal segment contracted simultaneously, together with the pyloric canal, which promptly closed. This resulted in a retropulsive force, pushing terminal antral content back into the stomach. They concluded that "the function of the powerful terminal-antral contraction is chiefly that of retropulsion, not propulsion".

Whether or not these Type II contractions depend on antral innervation via the nerves of Latarjet is not, to the author's knowledge, known. It seems likely that they may be since the nerves of Latarjet are anatomically the most accessible ones and division of those nerves has already been shown to alter gastric emptying. Nevertheless, if those Type II contractions depend on antral innervation, then such motor activity would surely be altered by selective vagotomy resulting in unopposed propulsive peristalsis through the pylorus. A widely patent pylorus (after pyloroplasty) would offer no physical barrier to such peristalsis, resulting in faster emptying. Why an

increase in emptying on this basis was not observed after selective vagotomy alone is unknown. Clarke and Williams (1972) were able to demonstrate this initial rapid rate after selective vagotomy alone, but we, unfortunately, were not.

As a general rule, these emptying results may be summated by assuming that preservation of antral innervation is more important in itself than routine addition of a pyloroplasty but, once that innervation is destroyed, the physical state of the pylorus becomes critically important.

B. Gastric Secretion of Acid and Pepsin

1. Acid Secretion

a. Basal Acid Output

Resting secretion of HCl by the stomach was unchanged until the antrum was denervated. It is unlikely that this finding was due purely to a loss of nervous control since denervation of the parietal cell mass (highly selective vagotomy) had no appreciable effect. In order to explain these results, it is necessary to review the hormonal control of acid secretion and its proven interaction with nervous influences.

Gastrin is released from the antrum either by direct distention of its walls, by topical agents or by vagal stimulation, this last mechanism demonstrated by Pe Thein and Schofield (1959). In addition, according to Emas (1969), a "synergism" exists between the vagus and intrinsic or extrinsic gastrin and gastrin-like substances such that tonic vagal impulses appear to facilitate the release of gastrin from

the antrum. With these observations in mind, let us reexamine the operative procedures in general terms.

As previously mentioned in Chapter II, the technical performance of the operation of highly selective vagotomy is dependent on a knowledge of the anatomy of the vagus. Once in the operating room, however, the proper exposure and display of that anatomy is tantamount to success. As a result, a considerable amount of traction by pulling and stretching, dissection and instrumental manipulation of the stomach and its attendant structure may be incurred during surgery. This trauma raises the possibility of *neuropraxial injury to the nerves of Latarjet* during the performance of highly selective vagotomy.

Consider then the results of those authors who report a decrease in basal secretion. If, in fact, neuropraxia of the nerves to the antrum had been incurred at surgery, they would in actuality be reporting the results of an inadvertent selective vagotomy, not a highly selective one. Why associated changes in emptying did not occur in these reports is not immediately clear, but suffice it here to say that results of emptying in these studies were generally given second seat to secretion results and those reports of emptying that are generally subjective, poorly controlled radiological studies.

The surgical technique used in this study was a strict "no-touch" one with reference to the nerves of Latarjet, the vagal trunks and the hepatic and celiac divisions. It is therefore with much interest that we note in our results that a decrease in basal acid secretion did not occur in our animals until the nerves to the antrum were deliberately cut and the decrease so achieved was of the

magnitude of that reported by other authors after highly selective vagotomy.

b. Pentagastrin-Stimulated Maximal Acid Output

The results of this study indicate that maximal acid secretion also did not change significantly until the nerves to the antrum were cut. The observed decrease of 43.7% in pentagastrin-stimulated maximal acid output after selective vagotomy was somewhat less than the 51 to 72% decrease expected from a review of the literature (Amdrup and Jensen, 1970; Johnston and Wilkinson, 1970; Wilkinson *et al*, 1971; Amdrup and Kragelund, 1971; Johnston *et al*, 1972, 1973; Wastell *et al*, 1972; Imperati *et al*, 1972; Kragelund *et al*, 1972), but was nevertheless significant when compared to either control or post-highly selective vagotomy values.

It would appear that the normal interaction between gastrin and the vagus was preserved intact following highly selective vagotomy since no change occurred in acid secretion. If we assume that the highly selective vagotomy was "complete", i.e. that all the direct gastric branches were divided, the "neuropraxia" theory is quite compatible with the observed results.

If the innervation to the gastrin-containing cells were intact and the normal interaction between nerve and hormone were present, as it should be after highly selective vagotomy, acid secretion should be normal and should only decrease when the neural component was lost - after selective vagotomy. If however, antral innervation was damaged during highly selective vagotomy, the reported postoperative acid secretion would necessarily be lower than normal - as it was in the

reports quoted.

An interesting corollary of this explanation concerns the function of the direct gastric branches. During this whole project, the author was unable to demonstrate a single physiological function which could be attributed to them. Is it possible they are entirely unconcerned with either secretory or motor activity and serve some other undisclosed function?

2. Pepsin Secretion

As with maximal acid output, pepsin secretion under pentagastrin stimulation did not change until the selective vagotomy stage when it decreased significantly.

Pepsin secretion and activity is known to be pH-dependent so it follows that a reduction in total acid output would cause a corresponding drop in pepsin secretion, as it occurred in our studies.

3. Discussion of the Insulin Test Results

It is possible that almost the entire battery of test results following highly selective vagotomy could be explained as surgical misadventure and failure to completely denervate the parietal cell mass.

At least, interpretation of the insulin test results would indicate this may be so. According to the criteria used, not a single animal was ever completely denervated, let alone after highly selective vagotomy. However, it is impossible to place much faither in a test which qualitatively yields such ambiguous results. Neither late positive preoperative tests nor conversion of late positive to early

positive results within the space of a few weeks are explicable.

Having become somewhat disillusioned by the results of this test, it is easy to point out its shortcomings. The test is based on completely arbitrary criteria worked out in animal experiments and transplanted virtually *in toto* to clinical work; it is open to argument and constant modification; it is inherently dangerous and, finally, it is notoriously unreliable in predicting recurrence. By way of example of the last statement, in five recurrent ulcers reported after highly selective vagotomy, one was early positive, and one was late positive and three were negative (Hedenstedt *et al*, 1972; Wastell *et al*, 1972). Fourteen recurrences after selective vagotomy with pyloroplasty were composed of three early positives, five late positives and six negatives (Kallehauge and Amdrup, 1969; Marckmann *et al*, 1969; Kronberg *et al*, 1970).

What of conversion of negative to positive insulin tests after highly selective vagotomy? The most widely accepted theory at present is that of vagal reinnervation (Johnston *et al*, 1973). However, agreement on whether or not such reinnervation occurs is not universal. Legros and Griffith (1970), using the vagal stimulation/neutral red technique in a small number of dogs, concluded that vagal reinnervation even after 12 to 15 months was "insignificant".

The "neuropraxia" hypothesis fits nicely with this observed high rate of reversion. If the nerves of Latarjet were damaged at highly selective vagotomy, gastrin release would be decreased as would consequent acid secretion resulting in negative responses. Healing of the traction injury with time would return the response toward

positive. If this explanation were true, one would expect the insulin test to change to negative following selective vagotomy. Unfortunately, it did not. In retrospect, the obvious test that was necessary was a transthoracic truncal vagotomy followed by a repetition of the insulin test but if this were done, the opportunity to examine the completeness of the original highly selective vagotomy would have been lost.

The quantitative analysis of the insulin test was similarly unhelpful. Even the values of basal acid secretion obtained prior to insulin injection are inconsistent when viewed in the light of the pre-pentagastrin basal values. In view of these inconsistencies, it would be premature to base any conclusions on this test without further experimentation. Consequently, it seems more sensible to judge the validity of each operation on findings using other techniques.

4. The 2-deoxy-D-glucose/Neutral Red Test of Completeness

Where the results of the insulin test might be interpreted to indicate that the original highly selective vagotomy in each of the ten animals was incomplete, the results of the terminal studies with 2-deoxy-D-glucose and neutral red dye indicated that at least seven of the ten animals were "completely" vagotomized. Only 5% or less of the total parietal cell mucosal area stained and very few large, overlooked nerve fibers were found, even in the three animals with more than 5% dye secretion. The poor correlation with the insulin results makes it impossible to decide which test to believe.

C. Conclusions

With reference to the objectives of this project outlined in Chapter I:

(1) Highly selective vagotomy is ineffective in reducing basal acid output and has no effect on either maximal pentagastrin-stimulated acid output or pepsin secretion.

(2) Highly selective vagotomy is effective in maintaining normal gastric emptying of liquids. The argument regarding the routine use of a complementary drainage procedure would appear to be an academic one since emptying after the two operations is virtually the same.

(3) Highly selective vagotomy is ineffective in reducing insulin-stimulated secretion and the qualitative results of the insulin test indicate the operation is ineffective in denervating the parietal cell mass.

(4) Selective vagotomy is far superior to highly selective in achieving decreased basal secretion and also reductions in maximal stimulated secretion and pepsin output. Its major disadvantage is a prolongation in the rate of gastric emptying which is somewhat over-compensated for by the addition of pyloroplasty.

(5) The results obtained indicate that the nerves of Latarjet to thegastric antrum play a major role in the regulation of both gastric emptying and gastric secretion of acid and pepsin.

Some additional comments seem warranted:

(1) The qualitative interpretation of the insulin test is of questionable value as a measure of the completeness of vagotomy.

(2) The results presented leave the function of the direct gastric branches of the vagus in doubt. They have been shown to have no appreciable effect on either gastric emptying or secretion of acid and pepsin. Is it possible they are entirely afferent or serve some unappreciated secretory or motor function?

Finally, if one is justified in drawing conclusions from animal experiments and extending them to clinical situations, the following comments are warranted:

(1) Highly selective vagotomy may not justifiably be applied to patients with peptic ulcer in view of its failure to decrease both basal and stimulated acid secretion.

(2) Selective vagotomy alone causes significant gastric retention and should not be applied to patients without a complementary drainage procedure, regardless of the physical state of the pylorus and, finally,

(3) Selective vagotomy with pyloroplasty offers a "safe" alternative to truncal vagotomy with drainage, provided one is cognizant of an initial rapid emptying rate and takes the necessary steps to minimize the sequelae it may cause.

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